THE American Journal OF Gastroenterology

A Journal of Clinical Gastroenterology

VOL. 70, NO. 1 JULY, 1978

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Significant gastric acid suppression means effective duodenal ulcer therapy



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Tablets, 300 mg. Injection, 300 mg./2 ml.

The H_2 Receptor Antagonist

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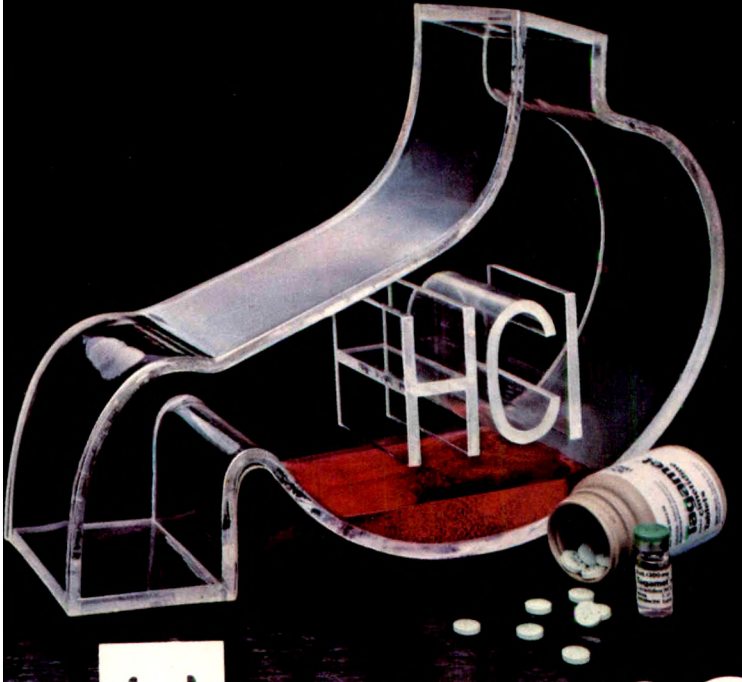
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1. Robinson AS, Sommer DA, Levinson M: Transfiberscopic removal of esophageal polyps. Am J Gastroenterol 61:297-300, 1974.

References to an article with *more than 3 authors:*

2. Starzl TE, Lee IY, Porter KA, et al: The influence of portal blood upon lipid metabolism in normal and diabetic dogs and baboons. Surg Gynecol Obstet 140:381-388, 1975.

Reference to a book:

3. Reuter SR, Redman HC: Gastrointestinal Angiography. Second Edition. Philadelphia, W. B. Saunders Company, 1977.

Reference to an article in a book:

4. Ansel HJ: Normal Pancreatic Duct. *In:* Atlas of Endoscopic Retrograde Cholangiopancreatography. Edited by Stewart, ET, Vennes JA, Geenen JE. St. Louis, The C. V. Mosby Company, 1977, pp. 43-47.

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HIGH-POTENCY ANTACIDS
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Total number of patients with endoscopically proved duodenal ulcer: 74
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1. Peterson WL, Sturdevant RAL, *et al*. Healing of duodenal ulcer with an antacid regimen. *N Engl J Med* 297:341-345, August, 1977.

*Antacid used was MYLANTA-II without its usual simethicone component.

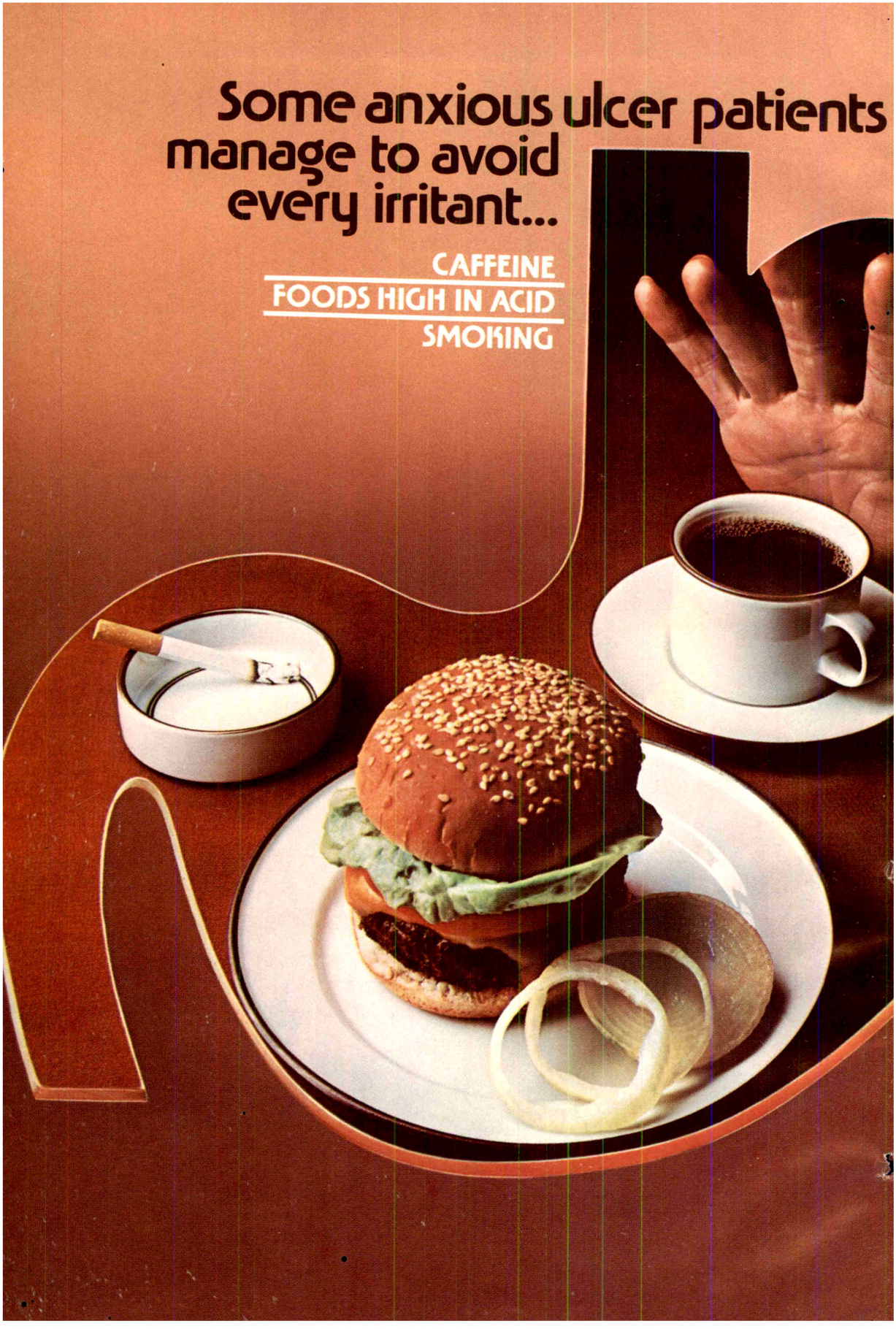
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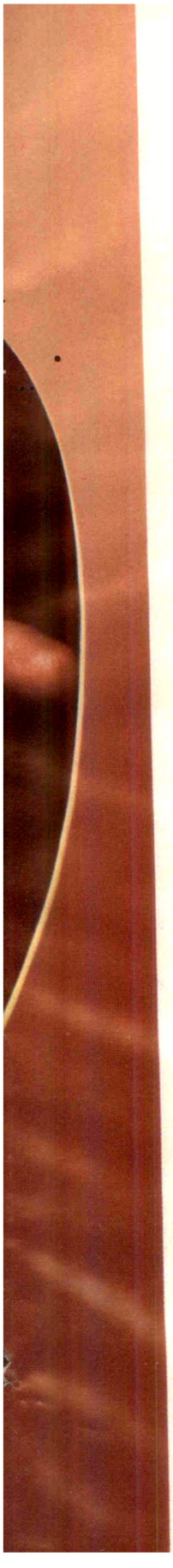
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Some anxious ulcer patients manage to avoid every irritant...
CAFFEINE
FOODS HIGH IN ACID
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ROCHE

...except excessive anxiety

While his ulcer is still in its active stage, the patient is usually quite scrupulous about following "doctor's orders." For the time being, at least, he's willing to forego coffee, alcohol, spicy foods, even cigarettes. But there's one irritant that some of these anxious ulcer patients may be unable to avoid—or to handle. Excessive anxiety.

For such patients, specific anti-anxiety medication is frequently indicated in addition to counseling and reassurance—that is where Valium (diazepam) comes in. Valium is a useful, highly dependable calming agent that works promptly to relax the patient and relieve his psychic tension and anxiety.

The characteristic response it produces is one that you know, want and trust.

Valium (diazepam) can particularly benefit the ulcer patient whose psychic tension increases at bedtime. The addition of an *h.s.* dose of Valium to a *b.i.d.* or *t.i.d.* regimen can reduce "nighttime" anxiety and thus may encourage sleep. At recommended dosages, Valium is usually well tolerated. Although drowsiness, ataxia and fatigue are sometimes encountered, these and more serious side effects are rarely a problem.

VALIUM®(IV)
(diazepam)

2-mg, 5-mg, 10-mg scored tablets

can relieve the ulcer patient's psychic tension and anxiety

Before prescribing, please see following page for a summary of product information

VALIUM®
(diazepam)

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not for sole therapy).

The effectiveness of Valium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

Supplied: Valium Tablets, 2 mg, 5 mg and 10 mg—bottles of 100 and 500; Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10; Prescription Paks of 50, available singly and in trays of 10.

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43rd Annual Convention, American Col of Gastroenterology, The Marriott, Den Colo., 24-27 September 1978.

Annual Course in Postgraduate Gastroe ology, American College of Gastroentero The Marriott, Denver, Colo., 28-30 Septe 1978.

One Day of Gastroenterology, Postgra Course co-sponsored by the American C of Gastroenterology, the Southern Medic sociation. Georgia World Congress Cente lanta, Ga., 11 November 1978.

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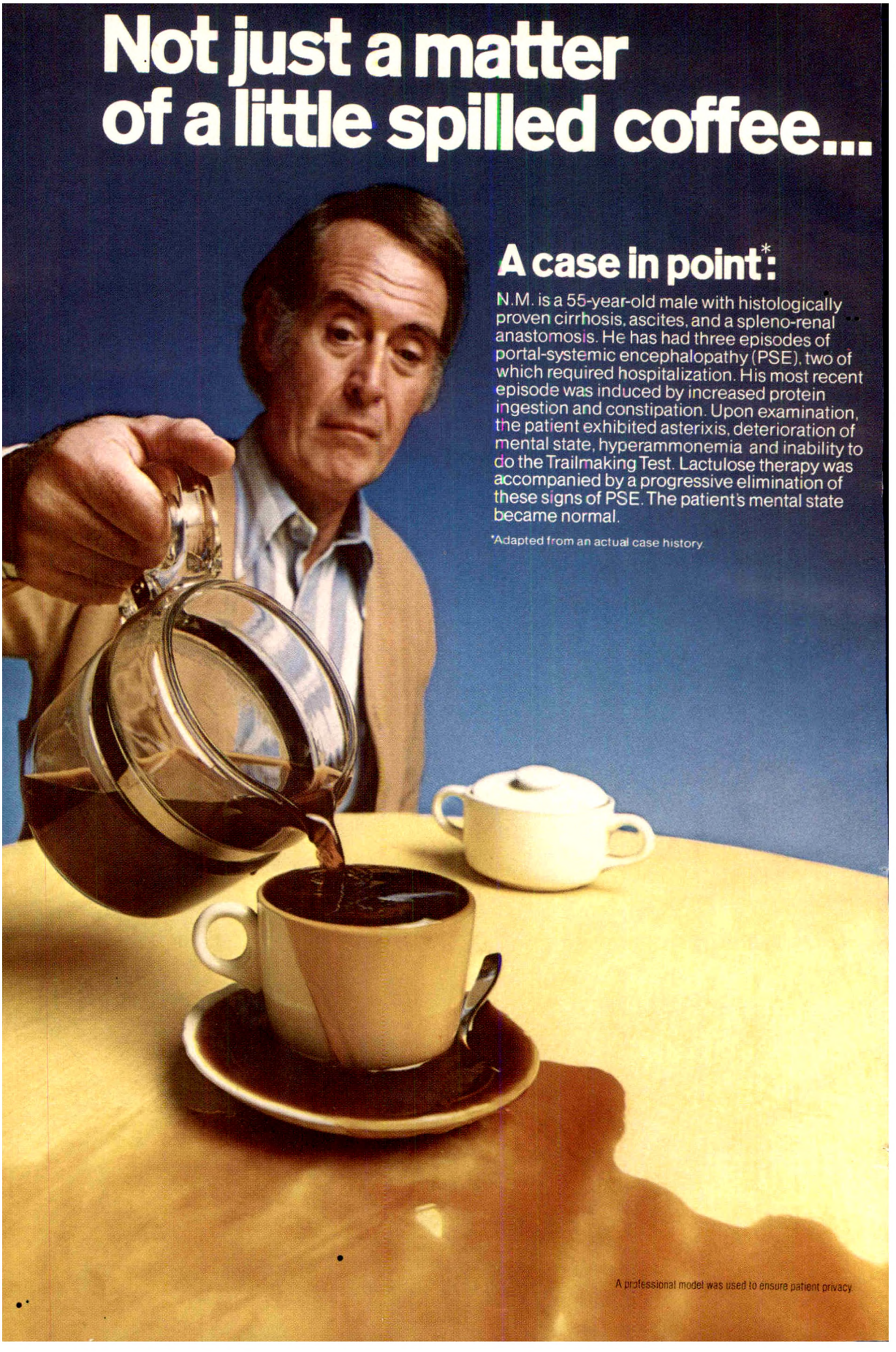
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A case in point*:

N.M. is a 55-year-old male with histologically proven cirrhosis, ascites, and a spleno-renal anastomosis. He has had three episodes of portal-systemic encephalopathy (PSE), two of which required hospitalization. His most recent episode was induced by increased protein ingestion and constipation. Upon examination, the patient exhibited asterixis, deterioration of mental state, hyperammonemia and inability to do the Trailmaking Test. Lactulose therapy was accompanied by a progressive elimination of these signs of PSE. The patient's mental state became normal.

*Adapted from an actual case history.

A professional model was used to ensure patient privacy.

this is portal-systemic encephalopathy (PSE)–

(Also called Hepatic Encephalopathy, pre-Hepatic Coma)

–a common complication of chronic liver disease.

Suspect PSE in every patient with cirrhosis.

Common early symptoms

- irritability
- euphoria
- lack of concern for others
- inappropriate behavior
- faraway look
- inversion of sleep pattern

Results of recent investigations of PSE

- Two-thirds of cirrhotic patients with portal hypertension who appeared mentally normal by conventional assessment revealed impairment of cerebral function on psychomotor testing. This dysfunction was in the same range as that in patients with brain damage after blunt trauma.[1]
- Alcoholic males with cirrhosis demonstrated a mental state significantly inferior to alcoholics without cirrhosis.[2]
- The majority of cirrhotic patients with portacaval shunts who appeared mentally normal had demonstrable psychomotor impairment.[3]

Treat PSE with Cephulac (lactulose) Syrup

- relieves PSE in 75% of episodes
- acts without serious adverse reactions
- lowers blood ammonia levels
- improves EEG and mental state
- permits more normal dietary protein intake
- provides an easy-to-manage means of long-term therapy

Cephulac®

(lactulose) Syrup

Each 15 ml. of syrup contains: 10 g. lactulose (and less than 2.2 g. galactose, less than 1.2 g. lactose, and 1.2 g. or less of other sugars)

for the prevention and treatment of PSE in your patients with chronic liver disease

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Brief Summary

INDICATIONS: For the prevention and treatment of portal-systemic encephalopathy, including the stages of hepatic pre-coma and coma. Controlled studies have shown that lactulose syrup therapy reduces the blood ammonia levels by 25-50%; this is generally paralleled by an improvement in the patients' mental state and by an improvement in EEG patterns. The clinical response has been observed in about 75% of patients, which is at least as satisfactory as that resulting from neomycin therapy. An increase in patients' protein tolerance is also frequently observed with lactulose therapy. In the treatment of chronic portal-systemic encephalopathy, Cephulac has been given for over 2 years in controlled studies.

CONTRAINDICATIONS: Since Cephulac contains galactose (less than 2.2 g. / 15 ml.), it is contraindicated in patients who require a low galactose diet.

WARNINGS: *Use in Pregnancy*: Studies in laboratory animals have not revealed a teratogenic potential of lactulose. The safety of lactulose syrup during pregnancy and its effect on the mother or the fetus have not been evaluated in humans. The physician and patient should understand that the possibility that lactulose syrup might cause damage to the human fetus cannot be excluded. Lactulose syrup should not be given during pregnancy unless, in the opinion of the physician, the possible benefits outweigh the possible risks.

PRECAUTIONS: Lactulose syrup contains galactose (less than 2.2 g. / 15 ml.) and lactose (less than 1.2 g. / 15 ml.) and it should be used with caution in diabetics. There have been conflicting reports about the concomitant use of neomycin and lactulose syrup. Theoretically, the elimination of certain colonic bacteria by neomycin and possibly other anti-infective agents may interfere with the desired degradation of lactulose and thus prevent the acidification of colonic contents. Thus the status of the lactulose-treated patient should be closely monitored in the event of concomitant oral anti-infective therapy. Other laxatives should not be used especially during the initial phase of therapy for portal-systemic encephalopathy because the loose stools resulting from their use may falsely suggest that adequate Cephulac dosage has been achieved. In the overall management of portal-systemic encephalopathy it should be recognized that there is serious underlying liver disease with complications such as electrolyte disturbance (e.g., hypokalemia) for which other specific therapy may be required.

ADVERSE REACTIONS: Cephulac may produce gaseous distention with flatulence or belching and abdominal discomfort such as cramping in about 20% of patients. Excessive dosage can lead to diarrhea. Nausea and vomiting have been reported infrequently.

DOSAGE AND ADMINISTRATION: The usual dosage is 2 to 3 tablespoonfuls (30 to 45 ml., containing 20 g. to 30 g. of lactulose) three or four times daily. The dosage may be adjusted every day or two to produce 2 or 3 soft stools daily. Hourly doses of 30 to 45 ml. of Cephulac may be used to induce the rapid laxation indicated in the initial phase of the therapy of portal-systemic encephalopathy. When the laxative effect has been achieved, the dose of Cephulac may then be reduced to the recommended daily dose. Improvement in the patient's condition may occur within 24 hours but may not begin before 48 hours or even later. Continuous long-term therapy is indicated to lessen the severity and prevent the recurrence of portal-systemic encephalopathy. The dose of Cephulac for this purpose is the same as the recommended daily dose.

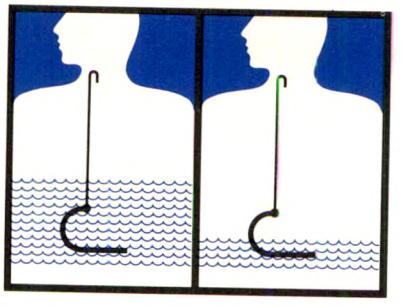
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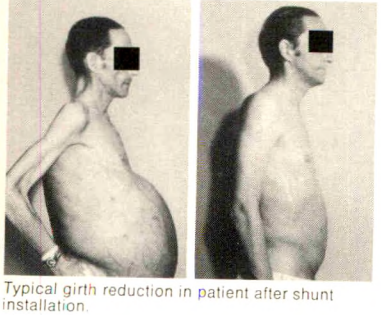
1. Schomerus, H. and Hamster, W.: Latent portasystemic encephalopathy. Digestion 14:548-549, 1976.
2. Smith, H.H. and Smith, L.S.: WAIS functioning of cirrhotic and non-cirrhotic alcoholics. J. Clin. Psychol. 33:309-313, 1977.
3. Rikkers, L., Jenko, P., Rudman, D. and Freides, D.: Subclinical hepatic encephalopathy: detection, prevalence, and relationship to nitrogen metabolism. Gastroenterology 72:1119, 1977.

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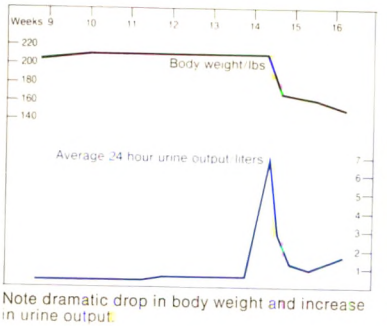




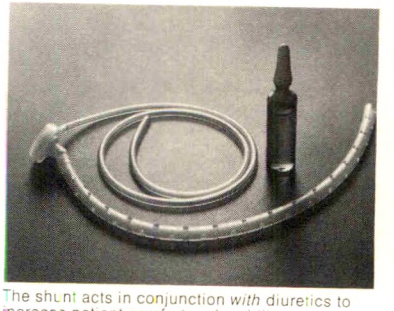
The LEVEEN Peritoneo-Venous Shunt.
A device that can contribute significantly to the medical treatment of refractory ascites.



Typical girth reduction in patient after shunt installation.



Note dramatic drop in body weight and increase in urine output.



The shunt acts in conjunction *with* diuretics to increase patient comfort and mobility.

Refractory ascites has traditionally been a medically-managed problem, often complicated by increased aldosterone, creatinine and BUN levels, reduced sodium clearance, and progressively increasing oliguria. The treatment of choice, which usually includes a salt-restricted diet and a regimen of powerful diuretics, eventually may only mobilize the ascitic fluid at the expense of renal function. The patient often requires repeated hospitalization as fluid becomes more and more difficult to mobilize, and increased girth, breathing difficulty, nutritional deficiency and renal complications reduce the patient's mobility, comfort and longevity.

Not a cure or a solution by itself, but, combined with diuretic treatment, a promising improvement in patient comfort and longevity[2].
Easily implanted, the LEVEEN Peritoneo-Venous Shunt offers another tool to simplify this usually difficult course of patient management. By means of a pressure-activated valve with attached tubing, the shunt routes fluid from the peritonel cavity into the superior vena cava. Thus by increasing the intravascular fluid, the shunt may help to prevent or actually reverse the hepato-renal syndrome[5], while it can allow a wider safety margin for the use of diuretics without causing kidney damage.

Urine output increased, girth reduced.
Studies have shown that patients with the shunt implanted usually present a drop in aldosterone, creatinine, and BUN levels, with increased sodium clearance, urine output, and reduced girth and body weight. All of these results usually occur within 24 hours after shunt installation.[1-3] In one 1977 study of 28 patients, mean urine flow increased from 607 ml to 4,254 ml, mean abdominal girth dropped from 108 to 93 cm, mean BUN level fell from 39 to 23 mg/100 ml, and the mean plasma creatinine level was reduced from 2.4 to 1.8 mg/100 ml[4].

More mobility, less hospitalization.
In the same 1977 study, most patients were discharged within 10 to 15 days after surgery, and after 18 months, nearly half were still alive. Of patients who had a bilirubin value of less than 10 mg/100 ml and no signs of severe encephalopathy or recent GI bleeding, 71% were alive after 18 months.[4] Even after shunt implantation, patients still require medical attention, but will not, in most cases, remain hospital-bound, and will require less of the physician's time. Increased patient comfort and reduced hospital dependency will restore some degree of mobility and normality to the ascitic patient.

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Indications For Use:
The LeVeen Peritoneo-Venous Shunt may be indicated when the patient does not respond promptly to intensive medical management.

The shunt is designed to eliminate the accumulation of ascitic fluid. Shunt placement should be considered for treatment of ascites complicating the following conditions:

1. Cirrhosis
2. Budd-Chiari Syndrome
3. Chylous Ascites
4. Nephrogenic Ascites
5. Biliary Atresia
6. Amyloidosis
7. Cryptogenic Ascites

Contraindications For Use:
In certain patients, the LeVeen Peritoneo-Venous Shunt will not be effective, or may be contraindicated because of secondary complications that outweigh its benefits. These conditions are:

1. **Peritonitis.** This should always be suspected when the peritoneal fluid is turbid. Peritonitis can occur without the usual signs and symptoms in patients with ascites.
2. **Esophageal Varices.** With A Recent History Of Bleeding. If ascites and variceal bleeding are present concurrently, treating the varices first may be indicated.
3. **Renal Failure.** The shunt will not reverse the renal damage in patients with acute tubular necrosis or other types of primary renal failure. A low urine sodium concentration may be the best indication that the tubules are functional and may respond to a shunt.
4. **Bilirubin level above 10 mg/dl**

Cautions:

1. **Esophageal Varices.** Without Recent Bleeding. In patients whose varices have been treated surgically, the shunt may be effective.
2. **Neoplastic Ascites.** The LeVeen Peritoneo-Venous Shunt has been used with success in patients with intractable ascites associated with primary or metastatic intra-abdominal neoplasms.[3] The use of the shunt in such patients requires weighing the shunt's potential benefits against the possible hazard of generalized dissemination of neoplastic cells which are commonly present in the ascitic fluid of these patients.
3. **Associated Cardiac Disease.** Cardiac patients may be sensitive to increased blood volume due to sudden recirculation of large quantities of ascitic fluid. Removal of accumulated ascitic fluid from the abdomen at the time of shunt placement may be indicated in such patients.

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[8] Wong, P. Y., Jarfeh, I. J., et al: Effect of Albumin, Saline Infusion and Peritoneo-Jugular Shunt On The Renin-Angiotensin-Aldosterone System In Patients With Refractory Ascites And Alcoholic Liver Disease. Abstracts of Papers, the American Association for the Study of Liver Diseases, Twenty-Eighth Annual Meeting, Chicago, Illinois, Nov. 1-2, 1977.

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INDICATIONS: Adjunctive therapy in the treatment of ulcerative colitis.
CONTRAINDICATIONS: Systemic fungal infections; during the immediate or early postoperative period following ileocolostomy.
WARNINGS: Prolonged use may cause systemic reactions. Do not delay needed surgery while awaiting response to medical treatment. Proper insertion of the enema tip is essential to prevent rectal wall damage. Increased dosages are indicated before, during and after unusually stressful situations. Signs of infection may be masked, and new infections may appear, along with decreased resistance and decreased ability to localize infection.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Adequate human reproduction studies have not been done with corticosteroids. In pregnancy, nursing mothers or women of childbearing potential, weigh the possible benefits of the drug against the possible hazards to the mother and the embryo or fetus. Observe infants born of mothers treated during pregnancy for signs of hypoadrenalism.

Elevation of blood pressure, salt and water retention and increased excretion of potassium, requiring dietary restrictions and supplementation, may occur. All corticosteroids increase calcium excretion. *Immunization procedures, especially against smallpox, should not be undertaken in patients receiving corticosteroids, because of the possible hazard of neurological complications and lack of antibody response.* Close observation and chemoprophylaxis are indicated in patients with latent tuberculosis or tuberculin reactivity.
PRECAUTIONS: Use with caution in cases of impending perforation, abscess or other pyogenic infection, fresh intestinal anastomoses, obstruction, extensive fistulas, and in the presence of active or latent peptic ulcer, diverticulitis, renal insufficiency, hypertension, osteoporosis, or myasthenia gravis. Surgical prognosis may be impaired by increased infection hazard. Administer larger dose of appropriate antibiotics if infection is suspected. Drug-induced secondary adrenocortical insufficiency, minimized by a gradual dosage reduction, may occur with prolonged therapy. This condition may persist for months after discontinuation of therapy; therefore, hormone therapy should be reinstituted during periods of stress. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently. Corticosteroids exhibit an enhanced effect in patients with hypothyroidism and cirrhosis and should be used cautiously in patients with ocular herpes simplex because of possible cornea perforation. Use the lowest possible dose to control the condition and institute a gradual dosage reduction as soon as possible.

Psychic derangement may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids. Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.
ADVERSE REACTIONS: Local pain or burning, rectal bleeding, and apparent exacerbations of the disease or sensitivity reactions may occur in rare instances. The following adverse reactions should be kept in mind whenever corticosteroids are given.
Fluid and Electrolyte Disturbances: Sodium retention; fluid retention; congestive heart failure in susceptible patients; potassium loss; hypokalemic alkalosis; hypertension. *Musculoskeletal:* Muscle weakness; steroid myopathy; loss of muscle mass; osteoporosis; vertebral compression fractures; aseptic necrosis of femoral and humeral heads; pathologic fracture of long bones. *Gastrointestinal:* Peptic ulcer with possible perforation and hemorrhage; pancreatitis; abdominal distention; ulcerative esophagitis. *Dermatologic:* Impaired wound healing; thin fragile skin; petechiae and ecchymoses; facial erythema; increased sweating; may suppress reactions to skin tests. *Neurological:* Convulsions; increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment; vertigo; headache. *Endocrine:* Menstrual irregularities; development of Cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirement for insulin or oral hypoglycemic agents in diabetics. *Ophthalmic:* Posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos. *Metabolic:* Negative nitrogen balance due to protein catabolism.
DOSAGE AND ADMINISTRATION: The usual course of therapy is one RECTOID enema nightly for 21 days.

Sigmoidoscopic examination and x-ray visualization are essential for adequate monitoring.
HOW SUPPLIED: Boxes of seven 60 ml (hydrocortisone 100 mg) disposable single dose bottles with lubricated rectal applicator tips.
IMPORTANT: See full prescribing information before administering RECTOID.

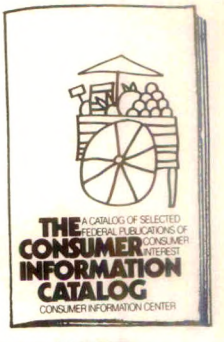
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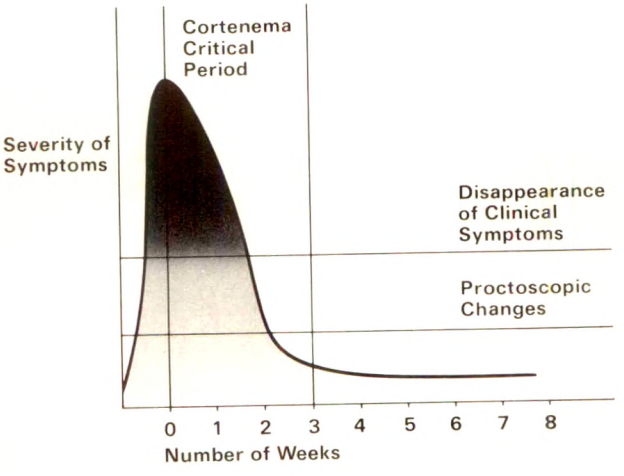
COMPOSITION: Each 60 ml. unit contains Hydrocortisone, 100 mg. in an aqueous solution of carboxypolymethylene, polysorbate 80, and methylparaben, 0.18% as a preservative.
INDICATIONS: Adjunctive therapy in ulcerative colitis; especially distal ulcerative proctitis, proctosigmoiditis, left-sided colitis; proved useful also in some cases involving transverse and ascending colons.
CONTRAINDICATIONS: Systemic fungal infections; recent ileocolostomy.
WARNINGS: In severe ulcerative colitis, avoid delay of needed surgery pending response to medical therapy. Careful insertion of enema tip is advisable to avoid rectal wall damage. Observe warnings of corticosteroid use; increase dosage of rapid-acting corticosteroids in unusual stress; corticosteroids may mask and decrease resistance to infection; prolonged use may predispose to cataracts, glaucoma, secondary ocular infections.
Usage in pregnancy: Pending adequate studies, corticosteroid use in pregnant, lactating or potentially childbearing women requires weighing possible drug benefits against potential hazards to mother and progeny. After large corticosteroid doses during pregnancy, observe neonates for hypoadrenalism.
Hydrocortisone or cortisone therapy may increase blood pressure, sodium and water retention, potassium excretion—effects less likely with synthetic derivatives, except in high doses. Salt restriction and potassium supplementation may be needed. All corticosteroids increase calcium excretion.
Avoid immunization procedures, including smallpox vaccination, during corticosteroid therapy, because of possible neurologic complications and lack of antibody response. Observe corticosteroid-treated patients with latent tuberculosis or tuberculin reactivity for signs of reactivated disease; provide chemoprophylaxis during prolonged corticosteroid dosage.
PRECAUTIONS: Use CORTENEMA cautiously in probability of bowel perforation, abscess or pyogenic infection, new anastomoses, obstruction, extensive fistulas or sinus tracts, and in peptic ulcer, diverticulitis, renal insufficiency, hypertension, osteoporosis and myasthenia gravis. Minimize hazard of adrenocortical insufficiency after prolonged treatment, by reducing dosage gradually and by adding mineralocorticoid and glucocorticoid support in post-treatment stress situations. In surgical infections during corticosteroid therapy, consider increasing antimicrobial dosage.
Use corticosteroids cautiously in hypothyroidism, cirrhosis and ocular herpes simplex; use aspirin cautiously with corticosteroids in hypoprothrombinemia. Psychic derangements may appear and emotional instability or psychotic tendencies may be aggravated with corticosteroid use. Carefully monitor growth of children on long-term corticosteroid therapy. Use the lowest effective corticosteroid dosage and reduce it gradually when possible.
ADVERSE REACTIONS: Local pain or burning, and rectal bleeding attributed to CORTENEMA have been reported rarely. Apparent exacerbations or sensitivity reactions also occur rarely. The following adverse reactions should be kept in mind whenever corticosteroids are given by rectal administration:
Fluid and Electrolyte Disturbances: Sodium retention; fluid retention; congestive heart failure in susceptible patients; potassium loss; hypokalemic alkalosis; hypertension. *Musculoskeletal:* Muscle Weakness; steroid myopathy; loss of muscle mass; osteoporosis; vertebral compression fractures; aseptic necrosis of femoral and humeral heads; pathologic fracture of long bones. *Gastrointestinal:* Peptic ulcer with possible perforation and hemorrhage; pancreatitis; abdominal distention; ulcerative esophagitis. *Dermatologic:* Impaired wound healing; thin fragile skin; petechiae and ecchymoses; facial erythema; increased sweating; may suppress reactions to skin tests. *Neurologic:* Convulsions; increased intracranial pressure with papilledema (pseudo-tumor cerebri) usually after treatment; vertigo; headache. *Endocrine:* Menstrual irregularities; development of Cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetics. *Ophthalmic:* Posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos. *Metabolic:* Negative nitrogen balance due to protein catabolism.
DOSAGE AND ADMINISTRATION: CORTENEMA should be used adjunctively with such supportive measures as dietary control, sedatives, antidiarrheal and antibacterial agents and blood replacement. The usual dosage, administered intrarectally in the evening before retiring, is 1 CORTENEMA per day for 2-3 weeks and every other evening thereafter until clinical and proctologic remission occur. CORTENEMA should be retained at least 1 hour or, preferably, all night and may be facilitated by prior sedative or antidiarrheal medication. Duration of treatment depends on both clinical and proctologic response. Clinical symptoms usually subside within 3-5 days; mucosal improvement may require longer, up to 2-3 months. Discontinue CORTENEMA if improvement fails to occur within 3 weeks.
HOW SUPPLIED: Single-dose 60-cc. bottles, in packages of 1 or 7, with instructions for patients.

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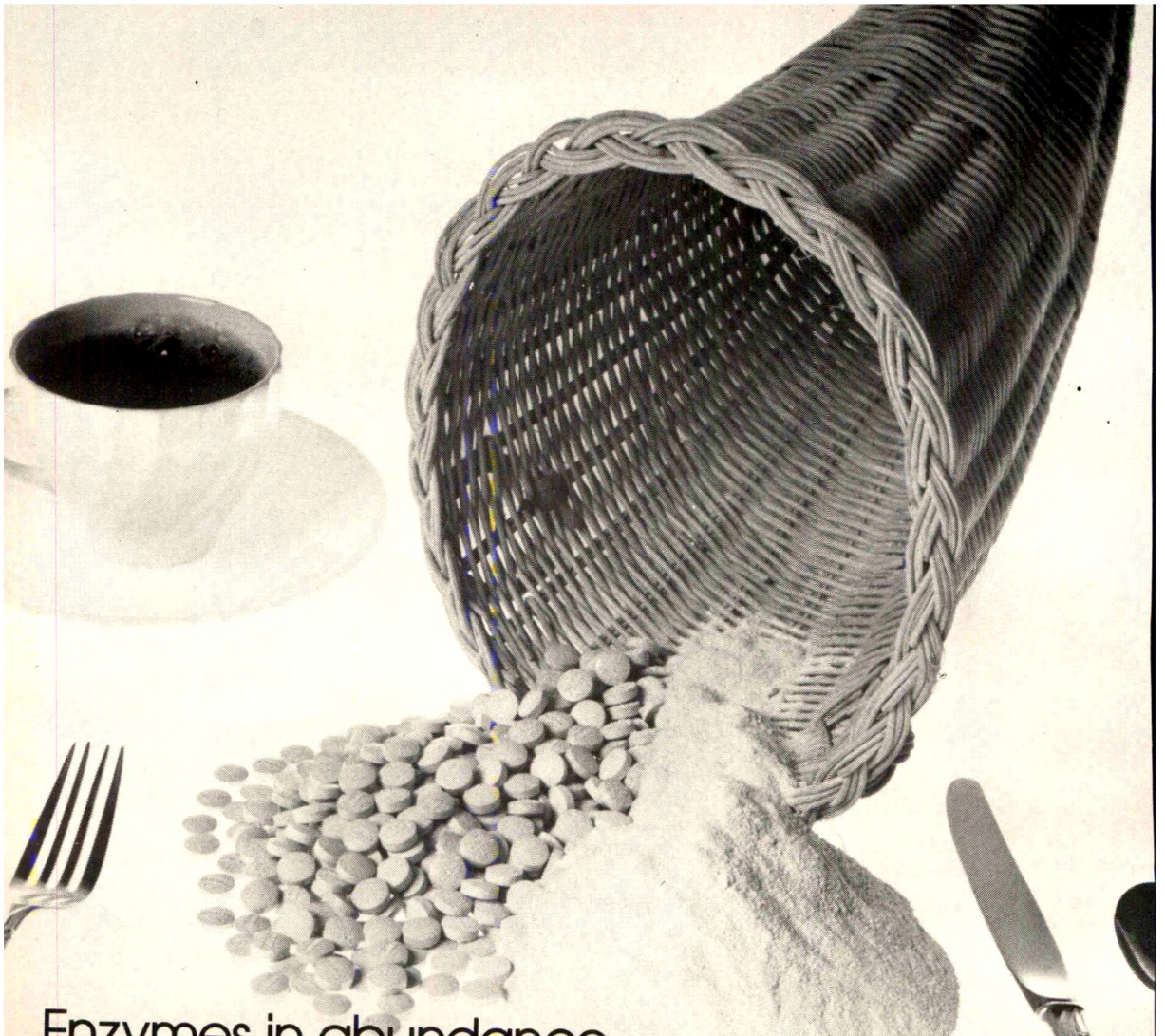


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Warnings: None.

Precautions: Use with caution in patients known to be allergic to pork protein.

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Efficient Manometric Technic for Accurate Regional Measurement of Esophageal Body Motor Activity

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WALTER J. HOGAN, M.D.
RONALD C. ARNDORFER
and
JOHN DENT, M.D.
Milwaukee, WI

We have developed a single station, manometric recording technic that allows quick and accurate measurement of motor activity occurring in all regions of the esophageal body. The manometric instrumentation features a catheter recording assembly with eight recording orifices spaced at uniform 3 cm. intervals. Each recording lumen is infused with water by a minimally compliant hydraulic-capillary system which achieves accurate recording of peristaltic and nonperistaltic motor activity in the esophageal body at an infusion rate of 0.5 ml./min. Because the recording sites of the manometric assembly span a distance of 21 cm., a distance which approximates the length of the esophageal body in humans, a detailed map of motor activity over the entire length of the esophageal body is achieved by securing the manometric assembly at one suitable portion. Because frequent repositioning of the manometric assembly is eliminated, the method described takes only a few minutes for comprehensive assessment of esophageal body motor activity.

In the past, manometric assessment of motor function in the esophageal body of humans often has been suboptimal because of the recording infidelity of conventional infused-catheter manometric systems and the tedious technics required to map motor activity over the entire length of the esophageal body. This report describes a quick, convenient method which permits accurate manometric recording of motor activity in all regions of the esophageal body. The method is applicable for both clinical and investigative studies.

From the Departments of Radiology and Medicine of The Medical College of Wisconsin.

This work was supported, in part, by a grant (PR–58) from the Clinical Research Centers Program of the Division of Research Resources, NIH, and by USPHS Research Grant No. RO1 AM 15540-04.

METHODS

A hydraulic-capillary infusion system, developed in our laboratory,[1, 2] allows high-

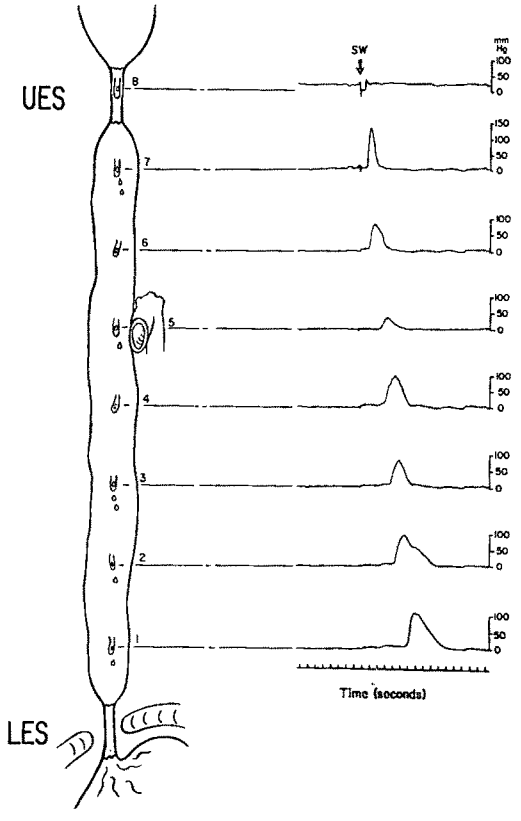


Fig. 1—Manometric recording of esophageal peristalsis in a normal subject. An esophageal peristaltic sequence is recorded over the entire length of the esophageal body. The manometric assembly used has eight recording sites spaced at 3 cm. intervals. Catheter 8, positioned within the upper esophageal sphincter (UES), monitors swallowing. This catheter was not infused because the patient experienced choking when fluid escaped into the pharynx. Catheters Nos. 7-1 record motor activity in all regions of the esophageal body. Catheters Nos. 7 and 5 record from the cervical striated-muscle portion of the esophagus; catheters Nos. 4-1, from the distal smooth-muscle esophageal segment and catheter No. 5, from an overlap zone of striated and smooth muscle near the level of the aortic arch. Swallowing elicits a peristaltic contraction wave which travels the entire length of the esophagus. Velocity of the peristaltic wave is greatest in the cervical esophagus and decreases as it moves distally. Correspondingly, wave duration increases in the distal esophagus. Amplitude of the peristaltic pressure wave is greatest in the proximal esophagus and a reproducible trough of low pressure exists near the aortic arch. Using only one assembly station, the manometric system shown in this figure permits high resolution of pressure events in all regions of the esophageal body.

fidelity recording of esophageal pressure waves using low infusion rates of 0.5 ml./min. or less for each manometric catheter lumen. Because the new infusion system is minimally compliant, negligible decreases in flow rate occur during dynamic pressure transients. Consequently, a rapid infusion rate is not needed to compensate for catheter compliance and to prevent the catheter orifice from sealing[3, 4] when the esophagus contracts. An important benefit of a low infusion rate is that catheters of small internal diameter (ID) can be used without incurring undue elevation of base line pressure caused by catheter resistance to flow.[5] Recording catheters with small ID's offer two important advantages over larger catheters: 1. they are less compliant than catheters of larger ID; consequently they yield a faster pressure rise rate following orifice occlusion[6] and 2. a greater number of catheters can be bundled together while still maintaining a manometric assembly of acceptable outside diameter (OD).[7] Based on these principles, we have developed a method for recording pressure accurately at close intervals along the entire length of the esophageal body.

For manometry of the esophageal body, we use a manometric assembly consisting of eight polyvinyl catheters, 130 cm. in length, each with an ID of 0.8 mm. and an OD of 1.8 mm. The catheters are fused longitudinally with tetrahydofuran around a supporting central polyvinyl catheter of 2.4 mm. OD. The diameter of the resulting assembly, about 6 mm., is small enough to permit comfortable nasal passage of the assembly in nearly all subjects. A side-hole recording orifice is cut in the eight individual recording catheters at 3 cm. intervals,

beginning 3 cm. from the end of the assembly. The resultant eight recording sites span a distance of 21 cm. A small metal marker is used to plug each catheter immediately distal to its recording orifice. The radial orientation of the recording orifices can be arranged so that the four distal and proximal recording sites, respectively, are axially oriented at equidistant 90 degree angles, thereby permitting four quadrant recording of esophageal sphincter pressure. The manometric catheters are connected to external force-displacement transducers which convert pressure changes into electric signals fed to an eight channel polygraph recorder. During pressure recording, each recording lumen is infused with boiled bubble-free water at the rate of 0.5 ml./min.

After the manometric assembly is passed via the nose into the esophagus, the lower and upper esophageal sphincters, respectively, are located by pull-through technic. The proximal recording site is then positioned within the high pressure zone of the upper esophageal sphincter (UES). Abrupt falls in UES pressure signal the onset of swallowing. Because the esophageal body in humans is generally 20-22 cm. in length the remaining seven recording sites of the manometric assembly record pressure events at 3 cm. intervals over the entire length of the esophageal body (Fig. 1). With the assembly secured at a single station, five to ten dry or wet swallows, or both, serve as a sufficient sample to map and quantitate esophageal motor activity for all regions of the esophageal body. This method accomplishes thorough examination of the entire esophageal body in about five minutes.

Comment

The manometric instrumentation and technic described in this report permit accurate recording of peristaltic as well as nonperistaltic esophageal motor activity occurring over the entire length of the esophageal body. Only one position of the manometric recording assembly is required to map motor activity for all esophageal body regions.

Since the early 1950's when esophageal manometry, using water-filled catheters, was adopted as a clinical method for studying esophageal motility,[8, 9] the traditional method for recording esophageal body motor activity has been a manometric assembly with three recording sites spaced at 5 cm. intervals. To map esophageal body motor function, such assemblies were often withdrawn through the esophagus in 1 cm. increments and swallows obtained at each station. Although this earlier method provided information about esophageal motor activity, the method was tedious and time consuming. Further, the data generated were difficult to analyze owing to the numerous assembly stations. Although some investigators added one or two additional recording catheters to their manometric assembly, the number of recording catheters remained limited by the need to keep the assembly diameter acceptably small.

Evolution of our present method for rapid, accurate assessment of esophageal body motor function depended on the development of a minimally compliant infusion system, which yields high-fidelity esophageal pressure recording at a relatively low infusion rate.[2] Because infusion rates of 0.5 ml./min. or less do not cause appreciable elevation of base line pressure in small catheters of 0.8 mm. ID, eight such recording catheters can be bundled together around a central supporting catheter without making the recording assembly unacceptably large. Numerous configurations of the side-hole recording orifices can be selected; however, the equidistant 3 cm. spacing described in this report yields an excellent assembly for studying esophageal body motor function.

During the past three years, we have used an eight lumen manometric assembly coupled with a hydraulic-capillary infusion system while performing more than 400 clinical manometric studies. This method yields accurate data in a minimum of time. We believe that the method is a useful tool for both clinical[7] and investigative[10, 11] studies of esophageal motor function.

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Gastric Carcinoma

A Critical Review of 243 Cases

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This review of 243 patients with gastric carcinoma includes 18.9% in TNM stage I, 8.2% in stage II, 26.3% in stage III and 46.5% in stage IV, 3.3% were early carcinomas. Age distribution was highest in the sixties (38.2%) and 85.2% were urban workers. Associated factors were alcoholism (26.7%), smoking (26.3%), benign gastroduodenal ulcers (14.4%), malignant tumors of the other organs (10.3%), family history of carcinoma (8.2%) and sideropenic anemia (4.5%). Predominant blood group was O (51.1%). There were 52.7% ulcerated, 36.6% polypoid or fungating and 10.7% diffuse or infiltrating adenocarcinomas. Predominant was antral (56.4%) pattern. Lesser curvature was a site of carcinoma 80.3%. Bone metastases were found in 7.8%. Reliable symptoms were weight loss (73.2%), epigastric, back or substernal pain (67.5%), hematemesis or melena (45.7%) and in carcinoma of the cardia or fundus—dysphagia or odynophagia (65.4%). Anemia was present in 51.6% and anacidity in 74.7%. Upper gastrointestinal series was diagnostic in 95.1%, esophagogastroscopy in 68.6%, gastric cytology in 71.0% and combined in all. Complications were bleeding (21.9%), obstruction (17.2%), bleeding and obstruction (7.0%), perforation (2.9%) and gastrocolic fistula (0.8%). Curative procedures were performed in 47.7% with 9.5% five-year survival which was 25.0% for stage I and 15.0% for stage II. Palliative procedures were done in 11.9%, diagnostic in 18.1% and none in 22.2% with no two-year survival. The five-year survival for proximal subtotal esophagogastrectomy was 10.0%, for total gastrectomy 7.7%, for distal subtotal gastrectomy 11.1% and for distal hemigastrectomy 6.2%. Over all five-year survival was 11 (4.5%) patients. There were 4.5% treated with adjuvant therapy with subjective and objective improvement in all. Primary cause of death in 72.0% was gastric carcinoma itself. Other primary cause of death was bronchopneumonia or lung abscess (5.4%), deep venous thrombosis and pulmonary embolism (4.6%), anastomotic or duodenal stump disruption (4.6%) and associated malignant tumors (4.6%). Misdiagnosis and delayed treatment occurred in 14.9%. Associated hiatus hernia was found in 1.6%. The Thal-Nissen procedure was carried out on distal esophageal stricture due to extention of adenocarcinoma of the cardia thought to be benign in one (0.4%) patient. None of them survived five years.

Worldwide gastric carcinoma still presents challenging and unresolved problems for the human population as a whole.[1, 2] The highest age-adjusted death rate per 100,000 in 1970-71 in Japan was 61.6 for male and 32.6 for female. In the U.S.S.R. (1966-67) it was 49.8 ranging from 64.3 in the North to 13.1 in the South. The U.S.

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male had (1970-71) age-adjusted death rate per 100,000 of 8.0 and female of 3.9. In spite of decrease in the incidence of gastric carcinoma in the U.S.A., it remains the fifth leading cause of cancer death in American males. Twenty-three thousand new cases (14,000 in male and 9,000 in female) and deaths of 6,900 (5,000 in male and 1,900 in female) were estimated for 1977 for the U.S.A.

The purpose of this report is to review epidemiological, etiological and associated factors, specially such as previous benign gastroduodenal diseases and synchronous or metachronous tumors of the other organs, believed to play a role in development of gastric carcinoma. Some aspects of the pathology, diagnosis, treatment and results as well as causes of death in patients with gastric carcinoma are presented. The other purpose is to show how much gastric carcinoma is neglected and to stimulate an effort for early diagnosis, better treatment and survival.

Clinical Material

This series consists of 243 patients with gastric adenocarcinoma treated at the Dayton Veterans Administration Hospital, between 1948-75. Gastric carcinoma was diagnosed clinically in 225 (92.6%) and at autopsy in 18 (7.4%) cases. Staging was based on TNM system (Table I). There were only eight (3.3%) early gastric carcinomas involving the mucosa and the submucosa (essentially T1 lesion), the rest 235 (96.7%) being locally advanced (T2-4).

Age distribution was the highest in the sixties—93 (38.2%) and in the fifties—55 (22.6%) patients. Similar data were reported by others.[3-8] There were 165 (67.9%) whites and 78 (32.1%) blacks. Almost all patients were males—242 (99.6%) with one (0.4%) female but only 0.5% of the total hospital admissions were females. True sex incidence in males is 70.0% and for females 30.0% with a recent trend toward an increase in the male.[4, 5] Epidemiological and associated factors, believed to play a role in our patients, are presented in Tables II, III and IV; pathology, localization and metastases in Tables V and VI, Tables VII and VIII summarize clinical findings, while Tables IX and X summarize laboratory findings. Results of treatment in relation to TNM stage are shown in Figs. 1 and 2. Finally primary causes of death are shown in Table XI.

TABLE I

Staging of 243 Patients with Gastric Carcinoma According to TNM System*

Stage	No. patients
I. T1-3, NO, MO	46 (18.9%)
II. T1-4, N1 or T4 only, MO	20 (8.2%)
III. T1-4, N2, MO	64 (26.3%)
IV. T1-4, NO-2, M1	113 (46.5%)
Total	243

Gastric tumor (T) confined to mucosa (T1), involving all layers (T2), extending through serosa with or without invasion of adjacent structures (T3), and diffuse or infiltrating (T4).

Lymph nodes (N) metastases absent (NO), present in adjacent (N1) and remote (N2) perigastric.

Distant metastases (M) absent (MO) and present (M1).

* Staging System for Carcinoma of the Stomach, 1971. American Joint Committee for Cancer Staging and End Result Reporting, Chicago.

Epidemiology and Etiology

It is believed that environmental coupled with genetic and familial factors may induce changes in gastric mucosa leading to carcinoma.[7, 9] Geographic influences could be related to decreased sunray exposure as distance from the equator increases, mineral composition of the soil and nutrition. A positive correlation has

TABLE II

EPIDEMIOLOGICAL AND ASSOCIATED FACTORS IN 243 PATIENTS WITH GASTRIC CARCINOMA

Environment: urban workers	207	(85.2%)
urban skilled	22	(9.0%)
farmers	14	(5.8%)
Habit: smoking	64	(26.3%)
alcoholism	65	(26.7%)
Blood group in 47 (19.3%) patients: A	17	(36.2%)
O	24	(51.1%)
B	6	(12.8%)
Family history of carcinoma	20	(8.2%)
stomach	10	(50.0%)
others	10	(50.0%)
Sideropenic anemia	11	(4.5%)
Hypertrophic or giant hypertrophic gastritis	2	(0.8%)
Benign gastroduodenal ulcers	35	(14.4%)
gastric ulcer	18	(7.4%)
duodenal ulcer	8	(3.3%)
suture perforated gastric ulcer	2	(0.8%)
suture perforated duodenal ulcer	1	(0.4%)
distal hemigastrectomy for gastric ulcer	1	(0.4%)
distal hemigastrectomy for duodenal ulcer	3	(1.2%)
gastrojejunostomy (G.J.) for duodenal ulcer	1	(0.4%)
B.T.V. + G.J. for prolapsed antral mucosa	1	(0.4%)
Associated tumors	49	(20.2%)
benign	24	(9.8%)
malignant	25	(10.3%)

TABLE III

BENIGN TUMORS ASSOCIATED WITH GASTRIC CARCINOMA IN 24 (9.9%) PATIENTS

Type of benign tumor	No. of benign tumors
Gastric polyp (single or multiple)	6 (25.0%)*
Thyroid adenoma	4 (16.7%)*
Colonic polyp	3 (12.5%)
Pituitary adenoma	2 (8.3%)
Renal adenoma	2 (8.3%)
Adrenal adenoma	1 (4.2%)
Liver adenoma	1 (4.2%)
Adenomyoma of prostate	1 (4.2%)
Mixed tumor of parotid gland	1 (4.2%)*
Ganglioneuroma of adrenal gland	1 (4.2%)*
Hemangioma of brain	1 (4.2%)
Hemangioma of liver	1 (4.2%)
Total	24*

* 4 patients in addition to gastric carcinoma had associated benign and malignant tumors.

been found between incidence of gastric carcinoma and recent use of cooked cereals, canned fruits, soup and salted fish while there is a negative association with vegetables containing ascorbic acid. Nitrosation of nitrate derived from a food grown on nitrate rich soil, drinking water and preservatives with production of ankylnitrosamines in the stomach is being considered as an etiological factor.[10] Nitrosation has been shown to be inhibited by refrigeration and ascorbic acid. Thus food refrigeration and higher intake of ascorbic acid could be related to the decreased incidence of gastric carcinoma.

Although the role of genetic factors is disputed there are reports of a 10.0% incidence of proximal gastric carcinoma in the Northern European families with excess blood group A, sideropenic anemia and achlorhydria.[7, 9, 11, 12]

Environmental and genetic factors may induce gastric mucosa to progress from its normal state of intestinal metaplasia, then atypical, precancerous and finally cancerous changes. Chances for a precancerous condition to turn into carcinoma are for gastric ulcer 19.7-30.0%, gastric polyps 17.3%, chronic atrophic gastritis 16.1%, hypertrophic gastritis 6.2-13.5% and giant hypertrophic gastritis 9.1%.[7, 11, 13, 14] The potential for the development of carcinoma after procedures of less than total gas-

TABLE IV

TWENTY-EIGHT MALIGNANT TUMORS ASSOCIATED WITH GASTRIC CARCINOMA IN 25 (10.3%) PATIENTS

Type of malignant tumor	No. of malignant tumors
Adenocarcinoma of prostate	4 (16.0%)*
Adenocarcinoma of colon	3 (12.0%)
Squamous cell carcinoma of lung	2 (8.0%)
Small (oat) cell carcinoma of lung	2 (8.0%)
Adenocarcinoma of lung	1 (4.0%)
Squamous cell carcinoma of esophagus	2 (8.0%)*
Transitional cell carcinoma of urinary bladder	2 (8.0%)*
Squamous cell carcinoma of tonsil	1 (4.0%)
Squamous cell carcinoma of pyriform sinus	1 (4.0%)
Lymphosarcoma of lung	1 (4.0%)
Papillary adenocarcinoma of thyroid gland	1 (4.0%)
Carcinoid tumor of duodenum	1 (4.0%)*
Insulinoma	1 (4.0%)*
Clear cell carcinoma of kidney	1 (4.0%)
Adenocarcinoma of endometrium	1 (4.0%)
Stem cell leukemia, reticulum type	1 (4.0%)
Myeloid metaplasia with myelofibrosis	1 (4.0%)
Basal cell carcinoma of nose	1 (4.0%)
Basal cell carcinoma of lip	1 (4.0%)
Total	28*

* B. E., 63-year old white male had triple asynchronous malignant tumor (adenocarcinoma body of stomach, transitional cell carcinoma of urinary bladder and adenocarcinoma of prostate). M.B.C., 53-year old white male, had quadruple synchronous tumors (adenocarcinoma cardia of stomach, squamous cell carcinoma middle and distal esophagus, carcinoid tumor of duodenum and insulinoma).

TABLE V

PATHOLOGY AND LOCATION OF GASTRIC ADENOCARCINOMA IN 243 PATIENTS

Pathology and location	No. of patients
Ulcerative	128(52.7%)
Cardia	7(5.5%)
Body	10(7.8%)
Antrum	111(86.7%)
Polypoid or fungating	89(36.6%)
Cardia	38(42.7%)
Fundus	7(7.9%)
Body	33(37.1%)
Antrum	11(12.3%)
Diffuse or infiltrating*	26(10.7%)
Superficial spreading	2(7.7%)
Linitis plastica	24(92.3%)

* 25 (96.2%) of diffuse or infiltrating adenocarcinomas involved the entire stomach with exception of one (3.8%) which was localized in the pyloric antrum (Fig. 5).

trectomy appears to be high[15-18] and even somewhat increased in patients with duodenal ulcer.[7, 19]

Low serum pepsin and hypoacidity were found in 3.5% patients of which 30.0% developed gastric carcinoma.[11] Serum gastrin was increased in gastric carcinoma patients as a result of antral stimulation by low HCl production from achlorhydria, pernicious anemia and chronic gastritis.[11] Low serum pepsin, high gastrin and hypoacidity may serve as a guide to selection of high risk patients for screening.

There were epidemiological and associated factors in our patients (Tables II and IV). We found that 85.2% were urban workers although no consistent gradient risk between urban and rural population was demonstrated by others.[9] We believe that smoking and alcoholism may play a role by inducing metaplastic and precancerous changes in gastric mucosa since not only did 26.0% of our patients have this habit but in addition some of these were afflicted by multiple primary carcinoma of the lung, oral cavity, esophagus and stomach as well.

TABLE VI

SITE OF METASTASES IN GASTRIC CARCINOMA BASED ON OPERATIVE OR AUTOPSY FINDINGS IN 243 PATIENTS

Site of metastases	No. of cases
Remote lymph nodes	178 (73.3%)
Intraperitoneal solitary or diffuse	112 (46.1%)
Liver	93 (38.3%)
Pancreas	41 (16.9%)
Lung and pleura	31 (12.8%)
Bone	19 (7.8%)
Adrenals	12 (4.9%)
Kidneys or urinary bladder	11 (4.5%)
Spleen	10 (4.1%)
Gallbladder or C.B.D.	10 (4.1%)
Heart and pericardium	6 (2.5%)
Pelvic seeding	5 (2.0%)
Skin, S.C. tissue and muscle	5 (2.0%)
Brain	3 (1.2%)
Thyroid gland	1 (0.4%)

TABLE VII

SYMPTOMS OF GASTRIC CARCINOMA IN 243 PATINETS

Symptoms	No. of patients
Weight loss	178 (73.2%)
Epigastric, back or retrosternal pain	164 (67.5%)
Hematemesis or melena	111 (45.7%)
Nausea and vomiting	107 (44.0%)
Anorexia	78 (32.1%)
Weakness	77 (31.7%)
Changes in bowel habit	36 (14.8%)
Dysphagia or odynophagia	34 (14.0%)
Dyspnea or cough	21 (8.6%)
Epigastric fullness	16 (6.6%)
Regurgitation	8 (3.3%)
Indigestion	7 (2.9%)
Belching	5 (2.0%)
Fever and arthralgia	4 (1.6%)
Heartburn	4 (1.6%)
Hiccough	3 (1.2%)
None	5 (2.0%)

It has been supposed, until recently that blood group A is predominant in patients with gastric carcinoma.[7, 12] Moreover, gastric carcinoma, in association with blood group A and achlorhydria, has a less favorable prognosis in individuals over 50 years of age, which should be considered a high risk category. Although this may be true in proximal gastric carcinoma in Northern Europeans it may not be correct as a generalization; recently an excess of blood group A was found to be small[3] or even in fact blood group O predominated (47.5%), followed by A (43.0%), B (9.0%) and AB (0.5%).[4] This was also true in our series where the most common blood group was O (51.1%), then A (36.2%) and B (12.8%).

The significance of multiple occurrences of gastric carcinomas or other neoplasms within a family is not clear. It may be coincidence alone.[7] It has recently been reported[4] in only 1.5%. It was higher in our series—8.2%.

In sideropenic anemia and achlorhydria carcinoma develops in the proximal stomach, tends to be polypoid, multiple, slow growing and of low malignancy.[7, 11] We found 11 (4.5%) patients with this condition and one (9.1%) of them had poorly differentiated ulcerative adenocarcinoma in the antrum.

We could find one (0.4%) case of hypertrophic gastritis and one (0.4%) case of giant hypertrophic gastritis which, in association with gastric carcinoma, was reported in only a few cases.[20] Previously diagnosed gastric disorders in patients with carcinoma of the stomach are as high as 26.1%.[21] This was true in this series where 14.4% patients had from two to 37 (average 12.7) years' history of gastroduodenal ulcers or prolapsed antral mucosa. The coexistence of duodenal ulcer and gastric carcinoma was found in 0.1% in respect to duodenal ulcers and in 0.7% in respect to gastric carcinomas.[19] In patients presenting

TABLE VIII

SIGNS OF GASTRIC CARCINOMA IN 243 PATIENTS

Signs	No. of patients
Epigastric tenderness	62 (25.0%)
Palpable abdominal mass	59 (24.3%)
Undernourishment or cachexia	50 (20.6%)
Hepatomegaly	36 (14.8%)
Abdominal distention	23 (9.5%)
Paleness	21 (8.6%)
Peripheral lymphadenopathy	19 (7.8%)
Fluid shifting	14 (5.8%)
Pelvic shelf	11 (4.5%)
Atrophic glossitis	11 (4.5%)
Jaundice	6 (2.5%)
Subcuticular nodules	5 (2.0%)
Paralysis or paresis	2 (0.8%)
Visible gastric peristalsis	1 (0.4%)
None	5 (2.0%)

TABLE IX

LABORATORY FINDINGS IN 243 PATIENTS WITH GASTRIC CARCINOMA

Type of study	No. of patients
Hematocrit	182 (74.9%)
normal	88 (48.3%)
moderate decrease 30-35%	37 (20.3%)
severe decrease below 30%	57 (31.3%)
Gastric analysis	79 (32.5%)
normal acidity	15 (19.0%)
anacidity	59 (74.7%)
hyperacidity	5 (6.3%)*

* Defined as basal acid output above 3 mEq./hr. for male and 1.5 mEq./hr. in female and maximal acid output above 15 mEq./hr. for male and 12 mEq./hr. in female (Dodsworth JM, Fisher JE: Surgical therapy of chronic peptic ulcer. Preoperative assessment, choice of operations, and consequences. Surg Clin North Am 54:529-547, 1974).

with apparently benign gastric ulcer a carcinomatous ulcer was found in 3.9%, fresh carcinoma in an ulcer in 0.5%, at a different site from the ulcer in 0.9% and unsuspected superficial spreading carcinoma in 5.4%.[22] In our series, benign gastric ulcer coexisted in 7.4% and duodenal ulcer in 3.3% with gastric carcinoma. Patients who have coexisting duodenal ulcer and gastric carcinoma show higher incidence of blood group A and diagnosis is a difficult one.[19] Therefore, patients with duodenal ulcer and blood group A should be screened for gastric carcinoma with cytology and early endoscopy.

There is growing evidence that surgical procedures for benign gastroduodenal ulcers create a premalignant condition with an incidence of gastric carcinoma 0.5-10.6%.[15-18] It tends to develop on the average at 20-28.6 years after Billroth I, Billroth II partial gastrectomy or gastrojejunostomy, more likely for benign gastric than duodenal ulcer. In patients with late postgastrectomy syndromes gastric stump carcinoma was found in 4.0%; it should be considered in differential diagnosis. Screening should include endoscopy and multiple biopsies of the gastric remnant.

We had three (1.2%) patients who developed gastric carcinoma nine, three and two years after suture of perforated gastric and duodenal ulcers. In a case where a cancer was diagnosed three years after the suture of a perforated gastric ulcer an intraoperative four quadrant biopsy was negative. Gastric remnant carcinoma developed in six (2.5%) patients with a time interval of 16-46, average 26.5 years (Fig. 3). In one patient preoperatively alkaline gastritis was diagnosed but at surgery gastric stump carcinoma was found. Seven (6.0%) of 116 patients, who underwent curative procedures for carcinoma of the stomach, developed postgastrectomy syndromes. Four (57.1%) were long-term, over 10-year survivors but in none of them was gastric remnant carcinoma found.

Multiple malignant tumors of the stomach and other organs occurred in

TABLE X

ESTABLISHMENT OF DIAGNOSIS IN 243 PATIENTS WITH GASTRIC CARCINOMA

Type of procedure	Total performed	Positive	False negative
1. Upper gastrointestinal series	206 (84.8%)	196 (95.1%)	10 (4.9%)
2. Esophagogastroscopy and biopsy	70 (28.8%)	48 (68.6%)	22 (31.4%)
3. Gastric cytology	38 (15.6%)	27 (71.0%)	11 (29.0%)
4. Combined 1 and 2	35 (14.4%)	35 (100.0%)	
5. Combined 1-3 and anacidity	6 (2.5%)	6 (100.0%)	
6. Liver scan	5 (2.0%)	5 (100.0%)	
7. Biopsy (liver, BM or LN)	10 (4.1%)	10 (100.0%)	
8. Paracentesis	2 (0.8%)	2 (100.0%)	
9. Exploratory laparotomy	189 (77.8%)	181 (95.8%)	8 (4.2%)*
10. Autopsy	135 (55.5%)		
11. Autopsy diagnosis only	18 (7.4%)		

* Presumed to be benign ulcer at the time of exploratory laparotomy by gross evaluation, false negative biopsy or no biopsy taken during suture perforated gastric ulcer.

3.6%.[7] Its role in the etiology of gastric carcinoma is unclear and controversial. The status of cellular immunity which could be responsible for this phenomenon was found to be depressed as determined by 2,4-dinitrochlorobenzene response and the Mantoux reaction in one[23] but normal as based on level of T-cells and distribution of HL-A antigen frequency, except in those who received prior radiotherapy, in another study.[24]

The incidence of associated synchronous or metachronous tumors in this series was 9.9% for benign and 10.3% for malignant. A triple or even quadruple primary gastric and other malignant tumors were found in six (2.5%) patients. Of six cases with gastric polyp, one (16.7%) had a focus of adenocarcinoma. By histology the most common associated tumor was adenocarcinoma of the prostate found in five (2.0%) and by location malignancies of the lung were found in six (2.5%) of our patients. Only two case reports were made on two primary malignancies of the lung and the stomach.[25, 26] Of two (0.8%) patients with squamous cell carcinoma of the esophagus one received radiotherapy prior to the development of gastric adenocarcinoma. The most unusual was an association of quadruple synchronous tumors (Table IV, Fig. 4). An insulinoma was diagnosed by numerous attacks of loss of consciousness and seizures, typical Whipple triad and at autopsy.

The incidence of multiple primary neoplasm is increasing.[26] It is important to be aware of this problem. In any neoplasm a diligent search should be made for precancerous or other neoplastic lesions at the time of diagnosis and in follow-up. Both primaries should be treated with a cure in mind. Also, in a case of two primaries in stomach and lung, a shadow in the lung should not be assumed to be metastatic until so proven. No patient should be re-

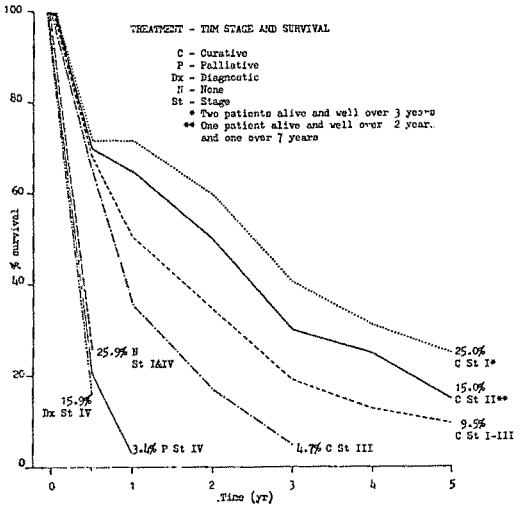


Fig. 1—Treatment-TNM stage and survival relationship in 243 patients with gastric carcinoma.

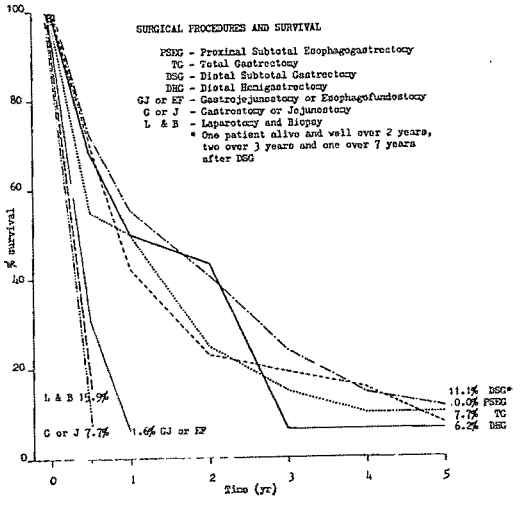


Fig. 2—Surgical procedures and results in 189 (77.8%) patients with gastric carcinoma.

fused the possible benefit of attacking surgically both primaries.

We found numerous diseases associated with gastric carcinoma. Arteriosclerotic cardiovascular disease in 111 (45.7%), chronic obstructive pulmonary disease in 69 (28.4%), pulmonary tuberculosis and cholelithiasis, each in 28 (11.5%), neuropsychiatric disorders in 20 (8.2%) and inguinal or umbilical hernia in 19 (7.8%). The first two call for careful cardiopulmonary care prior to, during and after surgery. A high incidence of chronic obstructive pulmonary disease in patients with gastric carcinoma and increased postoperative respiratory complications has been stressed.[4, 7] Benefit of expert pulmonary care is demonstrated in one of our patients, a 60-year old man, who had severe chronic obstructive pulmonary disease and while on constant respiratory support, including tracheostomy, underwent total gastrectomy because of bleeding adenocarcinoma of the cardia. There were no pulmonary complications in the postoperative period but he died 14 months later from respiratory failure.

Hiatus hernia with or without stricture in association with adenocarcinoma of the cardia occurred in five (2.0%) of our patients and carries a poor prognosis, since symptoms appear at late, incurable stages.[7, 27, 28] This was true in all of our patients. Two (0.8%) patients had herpes zoster and one (0.4%)—*Acanthosis nigricans.*

Pathology, Location and Metastases

Of 8,064 autopsies performed in our institution (1948-75) gastric adenocarcinoma was found 153 times, an incidence of 1.9%. A higher 5.2-5.4% has been reported.[29] Early gastric carcinoma was found in 15.5-25.0%[7, 30-33] but in recent Lahey Clinic data,[11] it was lower, 3.0-4.0%.

Grossly, gastric carcinoma may be divided into polypoid or fungating, ulcerative, and diffuse or infiltrating types (Table V).[7] The polypoid type is localized mainly in the proximal stomach and tends to be well differentiated, the ulcerative variety in the distal stomach and is moderately differentiated and infiltrating tumors as a rule, involve the stomach dif-

TABLE XI

PRIMARY CAUSE OF DEATH IN 243 PATIENTS WITH GASTRIC CARCINOMA

Primary cause of death	No. of patients	Mortality
	243	239 (98.3%)
Gastric carcinoma spread, recurrence or metastases	186 (76.5%)	172 (72.0%)
Associated malignancies	22 (9.0%)	8 (3.3%)
Gastric carcinoma and associated malignancies	3 (1.2%)	3 (1.3%)
Chronic obstructive pulmonary disease	69 (28.4%)	1 (0.4%)
Pulmonary tuberculosis	28 (11.5%)	1 (0.4%)
Bronchopneumonia or lung abscess	15 (6.2%)	13 (5.4%)
Pleural empyema	4 (1.6%)*	1 (0.4%)
Deep venous thrombosis and pulmonary embolism	19 (7.8%)	11 (4.6%)
Congestive heart failure	9 (3.7%)	8 (3.3%)
Myocardial infarction	4 (1.6%)	3 (1.2%)
Anastomotic or duodenal stump disruption	11 (4.5%)	11 (4.6%)
Subphrenic abscess	6 (2.5%)*	
Cholecystitis and cholangitis	3 (1.2%)	2 (0.8%)
Pancreatitis or pancreatic fistula	2 (0.8%)	1 (0.4%)
Stroke or head injury	4 (1.6%)	4 (1.7%)

* Three patients had pleural empyema and two had subphrenic abscess after disruption of esophagogastric anastomosis or duodenal stump. All died postoperatively and their death accounted under "anastomotic or duodenal stump disruption".

fusely and show poor differentiation. Of 218 (89.7%) gastric adenocarcinomas with precise location described, 45 (20.6%) were in the cardia, seven (3.2%) in the fundus, 43 (19.7%) in the body and 123 (56.4%) in the antrum. Thirty-eight (84.4%) of those located in the cardia, all of those in the fundus and 33 (76.7%) in the body were polypoid or fungating. In contrast, 111 (90.2%) of those in the antrum were ulcerated, 11 (8.9%) polypoid and one (0.8%) infiltrating *linitis plastica* type (Fig. 5). The rest of diffuse or infiltrating gastric carcinomas (96.2%) involved the entire stomach (Fig. 6). The tumor involves the lesser curvature three times more often than the greater curvature.[4] So it was in this series where the lesser curvature was the site of carcinoma in 53 (80.3%) and the greater in 13 (19.7%). Review of slides raised a question about the validity of a straightforward correlation between gross and microscopical appearance. Grossly fungating or polypoid or ulcerated tumor may contain an area of well or moderately differentiated intermingled with poorly differentiated adenocarinoma (Fig. 7). Anatomic location of gastric carcinoma is thought to follow an antral predominance pattern in Central and Eastern Europe, Asia, Africa and South America and an even distribution pattern in the rest of the world.[3-8, 11, 31, 34, 35] Our data fall into an antral predominance pattern, 56.4%. This

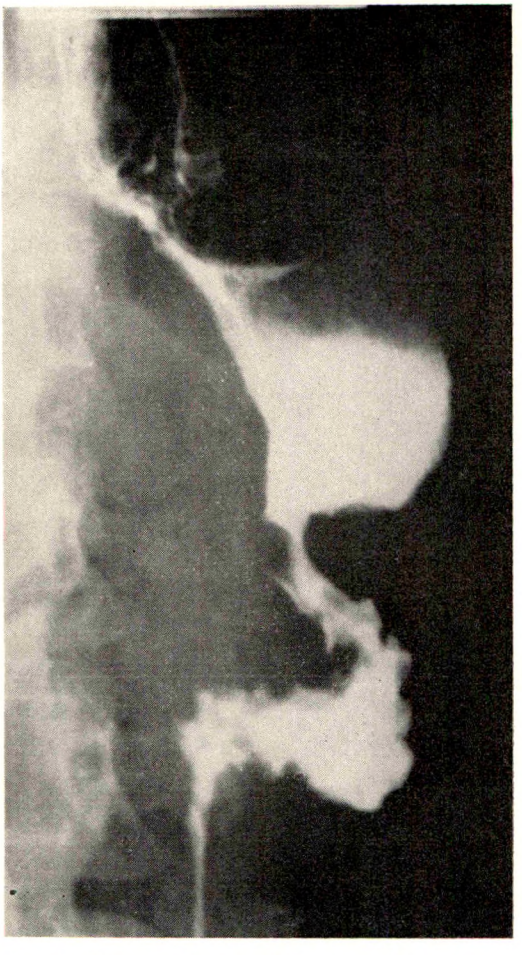


Fig. 3—Upper gastrointestinal series demonstrates adenocarcinoma of the gastric remnant 17 years after partial Billroth II gastrectomy for bleeding duodenal ulcer.

figure was not biased by blacks since 41 (58.6%) out of 70 had, similar to whites, an antral location. Likewise an incidence of diffuse or infiltrating carcinoma was 17 (10.3%) in whites and nine (11.5%) in blacks, an essentially equal value. Recent reviews from England[4] and Finland[6] show slight antral predominance.

Carcinoma of the pyloric antrum is believed to have the best prognosis.[4] This is not our experience since the best five-year survival was noted in three (7.0%) carcinomas located in the body. Six (4.9%)

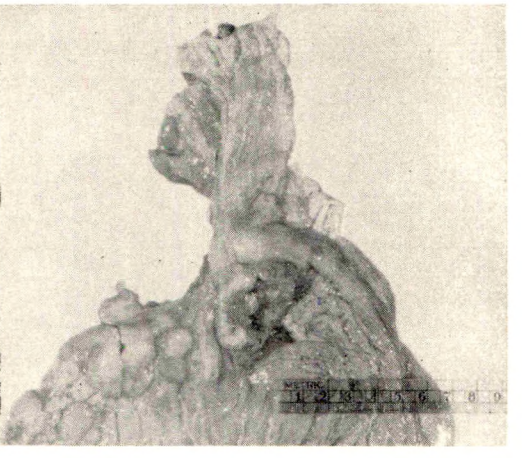


Fig. 4—Autopsy specimen shows synchronous adenocarcinoma of the cardia just below esophagogastric junction and transected squamuos cell carcinoma of the distal esophagus above and to the left.

with ulcerated carcinoma of the antrum and two (4.4%) polpoid or fungating of the cardia survived five years.

The metastatic pattern of our series (Table VI) in general parallels that reported by others.[7, 29] Bone metastases are considered a rarity but a true incidence depends on diligent search and ranges from 0-17.5.%[7, 36] Higher incidence was found in the German series[29]—19.9%. We were able to detect them in 7.8% (Table VI), including a case with metastases to the temporal bone (Fig. 8), manifested by a cochlear nerve dysfunction. The importance of bone metastases is that they may be a first sign of malignant gastric tumor or its recurrence and be easily mistaken for a primary bone tumor.[7, 36] After age 40 every bone tumor must be first approached as metastatic. Metastases to the temporal bone are treacherous causing considerable diagnostic difficulty and delay in treatment.

Clinical and Laboratory Diagnosis

Symptoms of gastric carcinoma are relatively reliable and any presented in Table VII signify need for further study.



Fig. 5—Specimen after distal subtotal gastrectomy for *linitis plastica* involving only the antrum.

The most significant in our and other series[3, 4, 7, 13] were weight loss, abdominal pain, hematemesis and melena, nausea and vomiting, anorexia, weakness, change in bowel habits, and in cases of carcinoma of the cardia or fundus—dysphagia or odynophagia (65.4%). Epigastric pain occurred in 69.0% patients who had precancerous conditions and preceded two to three, years' development of gastric carcinoma in 72.6%.[13] Intensity of the pain, however, decreased two to four months before establishment of the diagnosis, conceivably at the time of transition from precancerous to cancerous condition. Possibly gastric carcinoma secretes a substance which anesthesizes nerve endings or increases threshold of pain.

The relationship between onset of symptoms and survival is controversial. Most authors[4, 7, 37] believe that with the increasing duration of symptoms the chance for longer survival is greater while others[8] believe that a short history has a better prognosis.

In this series the interval onset-diagnosis for 12 (4.9%) patients was less than one month and for 36 (14.8%) patients between one to three months. There was no five-year survival in those two groups. Thirty two (13.2%) patients had an interval of three to six months and one (3.1%) survived five years. The best five-year survival—five (11.5%) was in a group of 42 (17.3%) patients with onset-diagnosis interval of six to nine months. Twenty-four (9.9%) had symptoms lasting nine to 12 months and one (4.2%) of them survived five years. The majority, however, 97 (39.9%) had symptomatology lasting over 12 months with four (4.1%) surviving five years.

Signs (Table VIII) were unreliable in diagnosing an early disease.

Complete blood count showed anemia in 51.6% (Table IX). This value is somewhat higher than the 43.0% reported.[3]

Experimentally gastric secretion was not changed by presence of carcinogen in the stomach or precancerous changes but developing cancer produced a considerable shift towards achylia.[38] Gastric carcinoma may coexist with normal or elevated acidity.[7] Most of our patients (Table IX) showed anacidity (74.9%), only few hyperacidity (6.3%). In one patient, a 42-year old man who had an ulcer crater of the antrum on the greater curvature and hypertrophic gastritis, gastric analysis was within range of the Zollinger-Ellison syndrome. He was seen in consultation by Dr. Robert M. Zollinger himself and underwent total gastrectomy. The pathological diagnosis was moderately differentiated ulcerative adenocarcinoma. He died four and a half years later from intra-abdominal metastases.

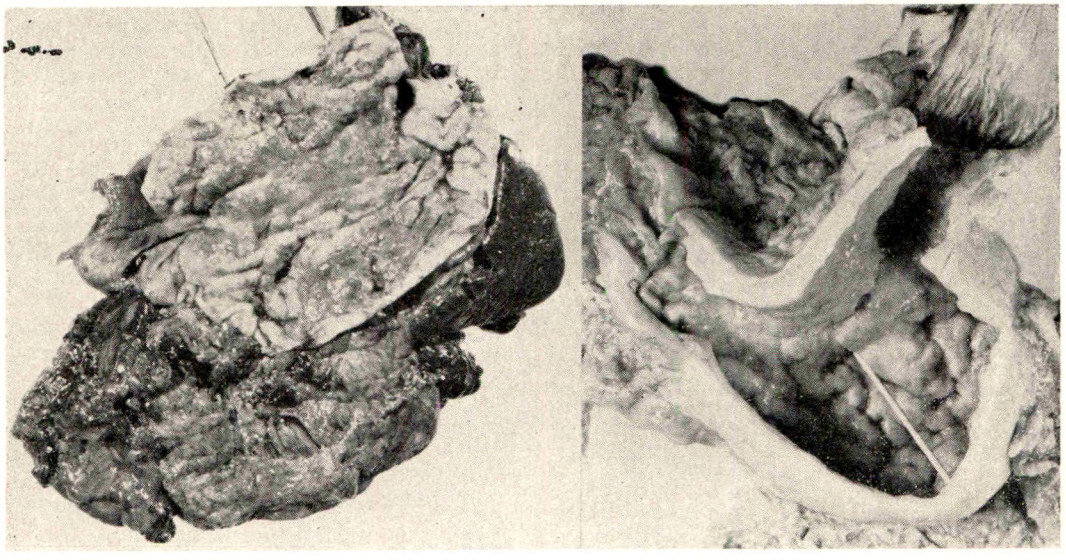


Fig. 6—Two types of diffuse or infiltrating gastric adenocarcinoma involving the entire stomach are presented. The one on the left is superficial spreading removed by extended total gastrectomy and the one on right is *linitis plastica* as seen at autopsy.

Class IV-V gastric cytology by washing is reliable in 46.4-90.2%.[5, 7, 39, 40] Any suspicious result should immediately be followed by endoscopy biopsy. Washing gastric cytology disclosed 6.7% gastric carcinoma including 0.2% of early neoplasia.[40]

Radiological examination of gastric masses should start from plain radiography of the abdomen which gives an estimated positive yield in 55.0%.[41] In one of our patients adenocarcinoma of the fundus was seen in an air-filled stomach in PA chest x-ray (Fig. 9). He survived 52 months after total gastrectomy. Reliability of an upper gastrointestinal series is 71.0-98.6%.[3, 5, 42] The reason for such varied accuracy is the difficulty imposed by determination of benignity or malignancy of gastric ulcers. The average radiological accuracy in diagnosis of ulcer, benignity is 99.5% while malignancy is 68.6%.[42] Radiologically projecting ulcers are usually benign but they should be followed until healed because secondary malignant ulcers, which account for the difference in accuracy, may have a similar appearance. By contrast intraluminal and shallow ulcers are often malignant.

Accuracy in the diagnosis of early gastric carcinoma is enhanced by double-contrast and hypotonic gastrography.[43, 44] The reliability of an upper gastrointestinal series in our series was 95.1% (Table X). Associated with gastric carcinoma, deformed duodenal bulb or duodenal ulcer, usually considered a rarity,[42] was found in eight (3.9%) patients.

Diagnosis of early gastric carcinoma has been improved since the introduction of fiberoptic esophagogastroscopy.[7, 31, 39, 45-47] Early endoscopy is a *sine qua non* in the evaluation of gastric ulcer and x-ray negative dyspepsia.[8] By fiberendoscopy gastric carcinoma was found in 13.8% patients and of those 9.5% on histology only and 5.8% in the early state.[45] A yield of positive endoscopy-biopsy ranges from as low as 50.0% to as high as 92.8%.[39, 46] Positive rates are increased to 95.0% when biopsy results from the rim and the slough of an ulcer are combined.[46] Endoscopic accuracy

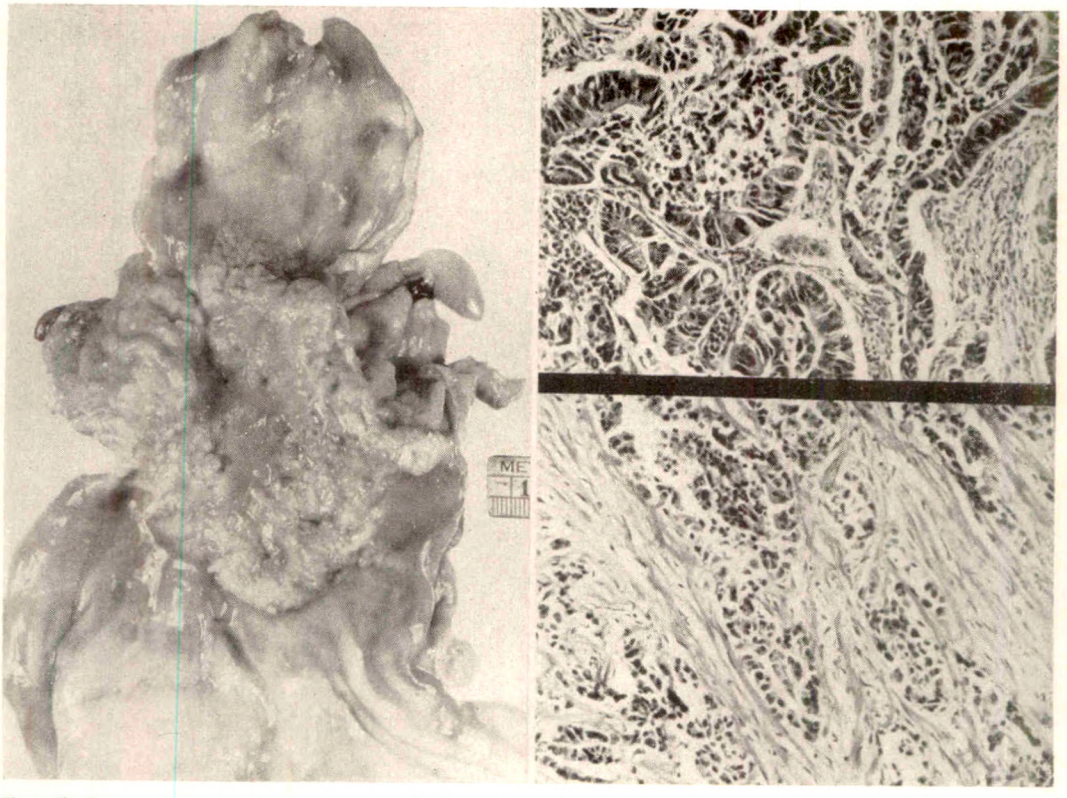


Fig. 7—Gross appearance at autopsy of fungating adenocarcinoma of the cardia (left) showing microscopically well differentiated adenocarcinoma in one area (right upper) and poorly differentiated in another (right lower).

could be further improved by indirect dye scattering with indigocarmine or methylene blue which intensify and delineate the mucosal surface.[48] Endoscopy increases the accuracy of gastric cytology by lavage (96.0%), by brushing (95.2%) and by imprint smear (85.7%).[39] Positive cytology values are higher in carcinoma of the cardia (90.0%) and in obstruction (92.0%).[47] Cumulative accuracy of esophagogastroscopy, multiple biopsies and brush cytology was 93.0%.[47]

At esophagogastroscopy it is important to determine esophageal involvement by carcinoma of the cardia which if extended 1 cm. above the esophagogastric junction calls for thoracotomy to permit radical operation.[49] If a mass, with or without ulceration, is present, as well as mucosal elevation or thickened mucosal folds in the lower esophagus there will be invasion 1 cm. proximal to the esophagogastric junction in 97.7%. Absence of these signs but a stenotic or asymmetrically open cardiac orifice indicates esophageal involvement 1 cm. from the esophagogastric junction in 43.5%. With a symmetrically open cardia no esophageal invasion was seen and this indicates that the abdominal route is sufficient.

In this series the reliability of esophagogastroscopy and biopsy (Table X) was in the low range (68.6%). Combined upper gastrointestinal series and endoscopy-biopsy alone or in addition to cytology and anacidity, however, were accurate in all cases. The value of combined radiological and endoscopical examination was empha-

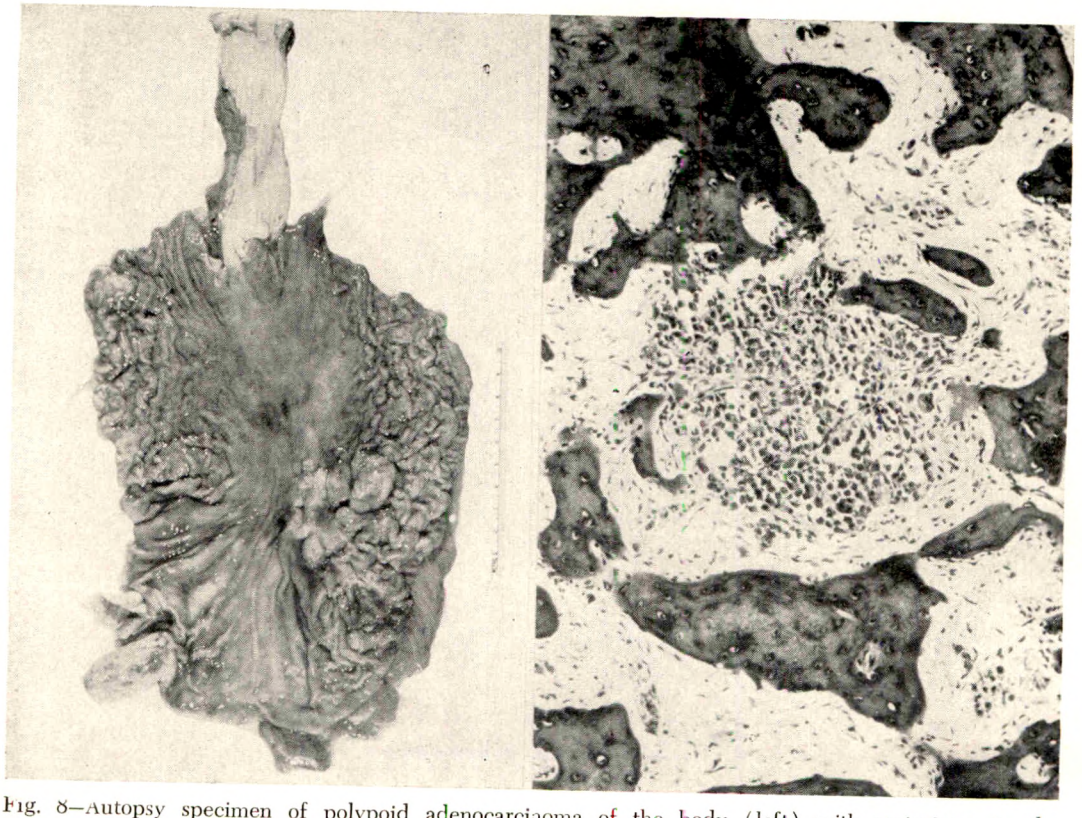


Fig. 8—Autopsy specimen of polypoid adenocarcinoma of the body (left) with metastases to the bone (right).

sized by mass screening for early gastric carcinoma.[50]

Of confirmatory diagnostic value were liver scan, biopsy of the liver, bone marrow or lymph nodes and paracenthesis as well as laparotomy and biopsy performed in 44 (23.7%) of 189 of all surgical procedures (Table X).

Helpful in staging and establishing criteria of inoperability are gastric scintigraphy,[51] ultrasonic B-scanning,[52] visceral angiography,[53, 54] and peritoneoscopy.[4, 7, 55]

Diagnosis by autopsy in 7.4% (Table X) was made on those admitted in extremis, unable to tolerate diagnostic procedures, those who died suddenly from other causes and were misdiagnosed.

Complications of gastric carcinoma in our series were bleeding in 53 (21.9%), obstruction in 42 (17.2%), bleeding and obstruction 17 (7.0%), perforation in seven (2.9%) and gastrocolic fistula in two (0.2%) patients.

Treatment and Results

The most important factors influencing five-year survival were stage of disease and mode of treatment (Figs. 1 and 2). The presence of lymph node involvement greatly worsened prognosis. It is often more extensive than apparent on the excised specimen.[4, 11]

Stages I-III should be treated by curative procedures: proximal location (cardia or fundus) by proximal subtotal esophagogastrectomy; mid portion location (body),

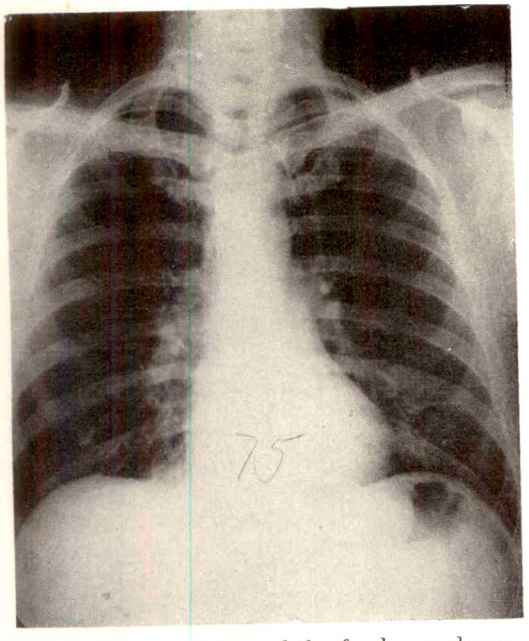


Fig. 9—Adenocarcinoma of the fundus as demonstrated by air-filled stomach on PA chest x-ray.

T4 or multiple lesions by total gastrectomy and distal location (antrum) by distal subtotal gastrectomy.[3-8, 11, 12, 21, 31, 32, 37, 56]

Stage IV should have some kind of palliative procedures in the form of nonradical resection or by-pass.[7, 8, 57, 58] Palliative resection increases mean survival time from seven to 19.4 months in stage III and from 5.6-15.5 months in stage IV and also, by virtue of removing the bulk of the tumor improves response to adjuvant therapy. Unresectable stage III (T3-4) and stage IV with obstruction at the cardia should have intubation (Celestin tube),[5, 6, 58] abdominal[59] or transdiaphragmatic[60] esophagojejunostomy; of the body—total gastric intubation (Häring tube) or fundojejunostomy[61] and in the antrum—gastrojejunostomy.

All gastric ulcers with unsuspected malignancy after partial gastrectomy should undergo revisional surgery within six to eight weeks.[35]

The treatment of choice for gastric remnant carcinoma is transthoracic total gastrectomy but in selected cases less radical procedures such as distal subtotal gastrectomy or wide excision are justified.[15-18]

Needless diagnostic laparotomy and biopsy should be avoided if criteria of inoperability can be established by other means.[4, 7, 51-55] The survival after laparotomy and biopsy was the lowest; only 15.9% survived six months. It is true that all submitted to laparotomy and biopsy were in stage IV and poor condition but postoperative mortality was not higher than in other procedures—20.4%. Perhaps immunological depression imposed by laparotomy and biopsy was great enough to shorten survival.

A "second look" laparotomy is indicated if local recurrence after curative procedures appears to be amenable for eradication.[7, 62]

Operability of all with gastric carcinoma varies 63.2-96.5% and resectability 32.0-70.0%.[3-6, 8, 11, 21, 37]

Curative procedures are performed in 41.4-49.8%, palliative in 13.0-15.7%, diagnostic in 21.2-37.2% including peritoneoscopy (1.3%) and none in 11.2%.[3-5, 32] Respective figures in this series were 47.7%, 11.9%, 18.1% and 22.2%. Proximal subtotal esophagogastrectomy is performed in 7.4-12.7%, total gastrectomy in 4.4-27.3%, distal subtotal gastrectomy in 22.8-60.0% and by-pass in 7.5-14.2%.[3-6, 21] Our data fall within these ranges: proximal subtotal esophagogastrectomy being carried out in 10.5%, total gastrectomy in 13.7%, distal subtotal gastrectomy in 28.6%, distal hemigastrectomy and by-pass each in 8.5%.

Postoperative mortality, defined as deaths within 30 days after surgery, is for proximal subtotal esophagogastrectomy 12.9%, total gastrectomy 11.3-18.2%, cur-

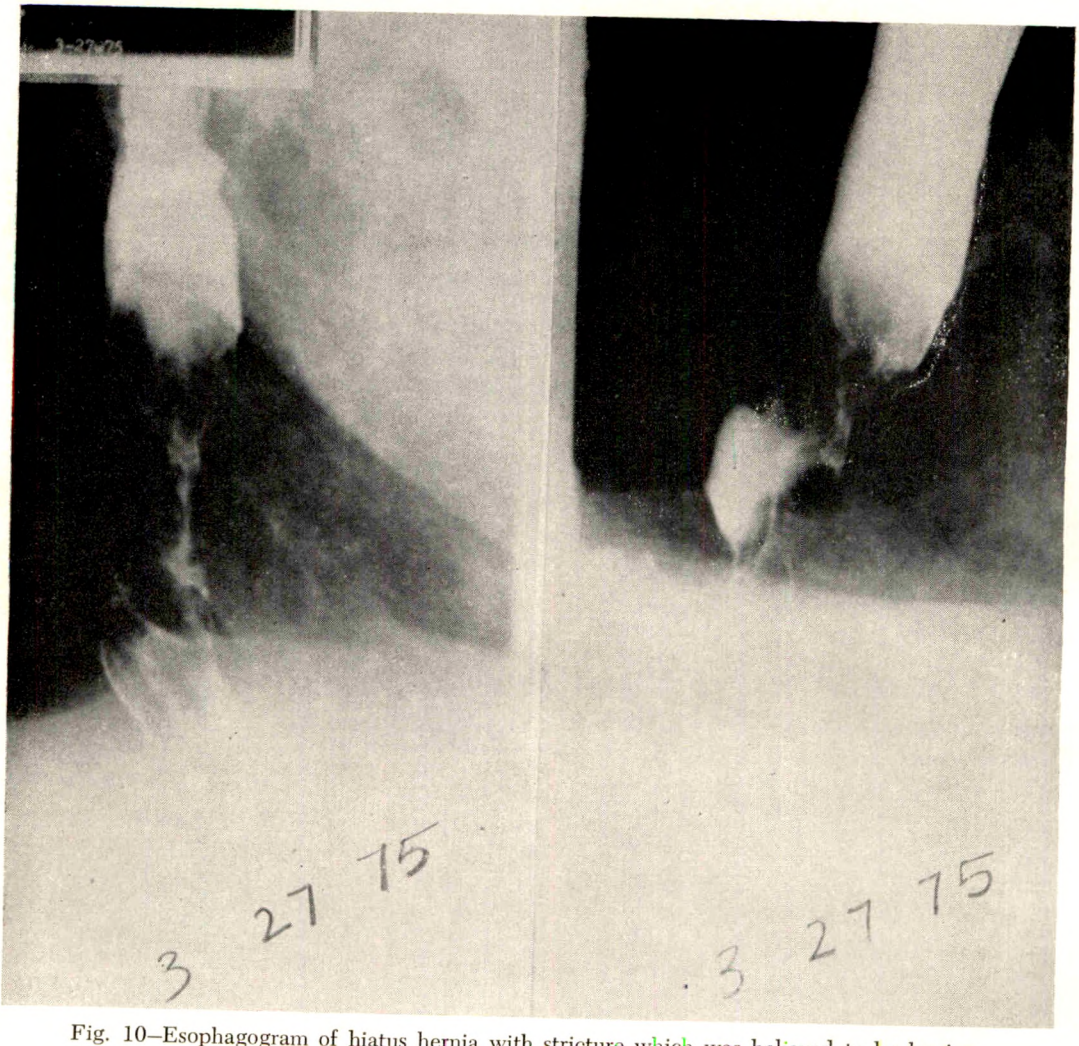


Fig. 10—Esophagogram of hiatus hernia with stricture which was believed to be benign.

ative distal subtotal gastrectomy 4.5-5.9%, palliative distal subtotal gastrectomy 11.4%, by-pass 18.1-19.4% and laparotomy and biopsy 8.9-15.6%.[3, 6, 21, 31, 37] In this series postoperative deaths were lower for proximal subtotal esophagogastrectomy (5.0%) but higher for the rest: total gastrectomy (23.1%), distal subtotal gastrectomy (18.5%), distal hemigastrectomy (12.5%), by-pass (31.5%), gastrostomy or jejunostomy (23.1%) and laparotomy and biopsy (20.4%).

Five-year survival after curative procedures is reported to range 16.2-43.0% and for palliative 0-7.0% being 4.3% for stage III and 1.1% for stage IV.[3, 4, 6, 8, 21, 37, 57] Our results were 25.0% for stage I, 15.0% for stage II, and none for the rest.

These results are poor when compared with five-year survival for early gastric carcinoma after curative procedures which is 58.0-96.3%.[30, 32, 33] Five-year survival for proximal subtotal esophagogastrectomy ranges 6.5-35.3%, for total gastrectomy 5.2-27.8% and distal subtotal gastrectomy 18.3-39.7%.[3-5, 21, 32, 37, 56] Our results fall into the above ranges for proximal subtotal esophagogastrectomy (10.0%) and total

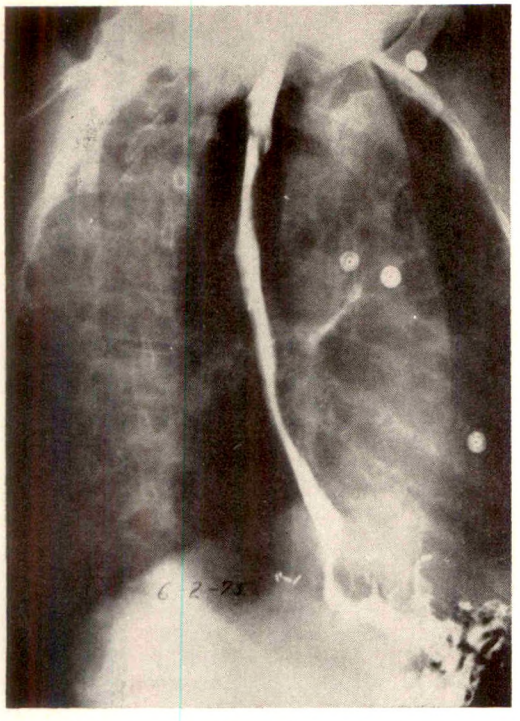


Fig. 11—Status post-Thal-Nissen procedure for distal esophageal stricture (Fig. 10). Single biopsy of stricture site was benign.

gastrectomy (7.7%) but were worse for distal subtotal gastrectomy (11.1%) and distal hemigastrectomy (6.2%).

The over all five-year survival for gastric carcinoma is still low 4.7-10.0%[3-5, 7, 8, 30, 56, 57] and it was low in our series (4.5%).

Adjuvant therapy for gastric carcinoma is in order.[7, 63] Preoperative gamma-therapy 25-31 MeV in fractional doses up to 2,000-3,000 r for stage I and 4,000-6,000 r for stage IV increased operability to 63.0-70.0% without increasing postoperative complications.[64] Combined preoperative telegamma-therapy 2,000-3,000 r followed by proximal or distal subtotal gastrectomy increased three-year and estimated five-year survival as compared to those treated only surgically.[44] A cure can be expected following intraoperative irradiation of 3,000 r with 8 MeV for stage III with unresectable remnant around major blood vessels.[65] Pathological examination of surgical specimens removed after preoperative treatment with fast neutrons showed, however, that macroscopic tumor can be eliminated but small clumps of tumor cells remained in the deeper layers in 97.5%.[66]

The best results from chemotherapy in stage III-IV were obtained when multiple drugs were used.[53, 67] With the use of 5-FU alone, objective effect was achieved in 18 ± 6.0% (life expectancy 5.2 months), with endoxan + vinblastin + methotrexate + 5-FU in 61 ± 10.0% (8.6 months) and of 5-FU + endoxan + methyl-CCNU + vinblastin + methotrexate in 70 ± 9.0% (9.2 months) patients. Others[68] had the best results with 5-FU + methyl-CCNU with 40.0% response and median survival 20 weeks. Over-all five-year survival, treated by preoperative intraarterial infusion chemotherapy and surgery, was 33.3% as compared to 29.7% of the controls.[69] Median survival treated by palliative nonresectional procedures of 2.9 months was increased by chemotherapy to seven months, by abdominal radiotherapy to nine months, by radiotherapy and chemotherapy to 6.1 months.[57]

We had experience with adjuvant therapy in 11 (4.5%) patients in stages III-IV. Curative procedures were combined with radiotherapy in one (9.1%) who survived 12 months; with chemotherapy in eight (72.7%) of which six (75.0%) survived 12 months and one (12.5%) five years. Palliative procedures plus chemotherapy were used in one (9.1%) surviving nine months and diagnostic procedures plus chemotherapy also in one (9.1%) with only three months survival.

Combination of intraperitoneal followed by oral administration of BCG and 5-FU + cyclophosphamide (stage IV) in-

creased mean survival in 62.5%, time interval being 11 months from diagnosis and 9.4 from the start of treatment.[70]

Cause of Death

The great majority, 172 (72.0%) of 239 died from gastric carcinoma itself (Table XI). Other significant primary causes of death were bronchopneumonia or lung abscess (5.4%), deep venous thrombosis and pulmonary embolism (4.6%), anastomotic or duodenal stump disruption (4.6%) and associated malignancies (4.6%).

There were contributing factors to death in 85 (35.0%); of those 72 died from gastric carcinoma itself.

Misdiagnosis and delayed treatment occurred in 36 (14.9%) contributing to death in 34 (14.0%). Only those patients are included here who at the time of misdiagnosis had enough symptomatology to suggest further work-up towards gastric malignancy. At fault were the medical staff 22 (61.1%), surgical 12 (33.3%) and both twice (5.5%). The reasons for misdiagnosis by the medical staff were prolonged conservative treatment of presumed duodenal or benign gastric ulcer in 12 (54.5%), digestive complaints thought to be of neuropsychiatric origin in five (22.7%), sideropenic anemia in two (9.1%) and hiatus hernia with duodenal ulcer in one (4.5%) patient. In addition, one (4.5%) was treated for pulmonary tuberculosis while no attention was given to abdominal symptoms; another (4.5%) simply did not have sufficient work-up. When the surgical staff was in error, a multitude of procedures were performed usually within one year or less prior to diagnosing stage IV. Most often it was inguinal herniorrhaphy alone or with other operations in six (50.0%). Among the remaining cases one (8.3%) of the following were performed on individual patients: thyroid lobectomy, dilatation distal esophageal stricture due to adenocarcinoma of the cardia, appendectomy, orchiectomy, TUR and laminectomy for back pain which in fact was radiating from gastric carcinoma. Finally in one (50.0%) the medical staff was treating duodenal ulcer while the surgeon performed inguinal herniorrhaphy and cholecystectomy overlooking a gastric mass; in another (50.0%) the internist was treating a malignant ulcer of the somach for months while the urologist was doing pancystoscopies and urethral dilatations.

Five (2.0%) patients had no symptoms or signs and four (1.6%) had associated hiatus hernia which masked early diagnosis. None of these nine (3.7%) survived five years.

False negative upper gastrointestinal series and esophagogastroscopy-biopsy delayed diagnosis in nine (3.7%) and six (2.5%) patients, respectively.

All eight (3.3%) who had false negative laparotomy (Table X) did not survive a significant length of time. Of these two (25.0%) had perforated carcinomatous ulcer. Perforated gastric ulcers are frequently malignant and multiple biopsy at operation or excision must be done.[4]

One (0.4%) patient who had a longstanding hiatus hernia developed distal esophageal stricture which was treated by the Thal-Nissen procedure while adenocarcinoma of the cardia was missed though a single intraoperative biopsy was done and reported as benign (Figs. 10-11). Chances of performing this procedure on malignant instead of benign stricture is 2.2%.[7, 27] Therefore, preoperative ciné-esophagogram and upper endoscopy-biopsy, thorough intraoperative palpation of the stomach and multiple biopsies rather than a single biopsy of a stricture with frozen and permanent secton are necessary.

In 13 (11.2%) of 116 patients who had curative procedures carcinoma was left in the line of resection and none of them (5.3%) survived five years.

Finally five (2.0%) refused surgery and died (0.8%) within less than a year.

Conclusions

Gastric carcinoma, although declining, still remains one of the leading causes of death throughout the world.

It is postulated that environmental factors, coupled with genetic and familial factors may induce atypical changes in gastric mucosa leading to malignancy.

Patients at high risk for gastric carcinoma are males in their fifties and over with blood group A or O, history of tumors in the family, with sideropenic anemia, gastritis and gastric polyps, hiatus hernia, gastric ulcer, with duodenal ulcer and blood group A, those who had previous distal partial gastrectomy, those with achlorhydria, elevated serum gastrin and decreased pepsin. To assure early diagnosis all such patients should be regularly followed up with upper gastrointestinal radiography, endoscopy-biopsy and cytology.

Patients with gastric carcinoma have a relatively high incidence of associated benign and malignant tumors of the other organs and should be screened for them.

Treatment for stages I-III should be proximal subtotal esophagogastrectomy for proximal gastric carcinoma, total gastrectomy for mid portion location and distal subtotal gastrectomy for distal lesions. Inoperable stage III and stage IV should have by-pass and adjuvant therapy.

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Comparison of Basal Gastric Acid and Pepsin Output in Controls vs. Active Peptic Ulcer Disease (PUD)*†

PRELIMINARY REPORT

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Quantitative basal and pentagastrin stimulated acid and pepsin outputs were determined in a group of 15 patients without peptic ulcer disease (PUD) and in 11 patients admitted to hospital with endoscopically proven PUD (two gastric and nine duodenal). While there were statistically significant differences in both acid and pepsin outputs in both the basal and maximally stimulated states, only the basal pepsin output clearly separated the groups in this small preliminary study. No patient produced more than 100,000 pU./hr. in the basal state unless an active peptic ulcer was present; no patient with an active ulcer produced less than 100,000 pU./hr.

Determination of gastric pepsin secretion or blood and urine levels of pepsinogen has never found a place in clinical medicine. The methods are time-consuming, subject to variable results with minor differences in technic and findings are expressed in many ways so that studies are difficult or impossible to compare. Further, these determinations in the past have not clearly discriminated disease states from nondisease.

More recently Samloff and co-workers, in a series of studies,[1-5] have made significant contributions to our understanding in this field and have crystallized confusing terminology. Their work has awakened new interest in pepsins and stimulated us to re-examine quantitative secretion of gastric pepsin in patients presenting with acute peptic ulcer disease. These data make up a preliminary report of our findings.

METHODS

We studied two groups of hospitalized patients. The nonulcer group was made up of 15 patients and included two asymptomatic volunteers and 13 with various medical problems but negative endoscopy. These 13 included four with functional bowel distress, three with reflux esophagitis, two with chronic renal failure on dialysis, one postrenal transplant on oral steroids, one postileal bypass for obesity, one six weeks after gastric irradiation for reflux esophagitis and one with systemic mastocytosis. This group is therefore not "normal controls". The acute ulcer group consisted of 11 patients who were admitted for symptoms related to acute peptic ulcer disease and all had endoscopically proven active ulcer disease (two were benign gastric ulcers; nine were duodenal ulcers). No patients had had gastric surgery.

After an overnight fast, a nasogastric tube was inserted into each patient in the gastroenterology laboratory and a one-hour basal collection obtained. Fluoroscopic placement of the tube was not done. Six 15-minute specimens were obtained after 6 μg. pentagastrin subcutaneously. Vol-

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‡ Professor and Director, Division of Digestive Diseases, University of Mississippi Medical Center.

TABLE I

BAO vs. PAO AND BPO vs. PPO IN NONULCER vs. ACUTE ULCER PATIENTS

Nonulcer		Acute ulcer	Significance	
		Acid (mEq./hr.)	T	
BAO(15)*	1.64 ± 1.28	(11) 9.96 ± 8.6	3.18	< .01
PAO(15)	19.95 ± 10.6	(9) 44.4 ± 10.1	5.63	< .001
		Pepsin (units/hr. × 10^3)		
BPO(15)	44.47 ± 25.9	(11) 192.4 ± 86.4	5.49	< .001
PPO(15)	314.6 ± 190.1	(9) 562.7 ± 119.2	3.01	< .01

* Number of observations

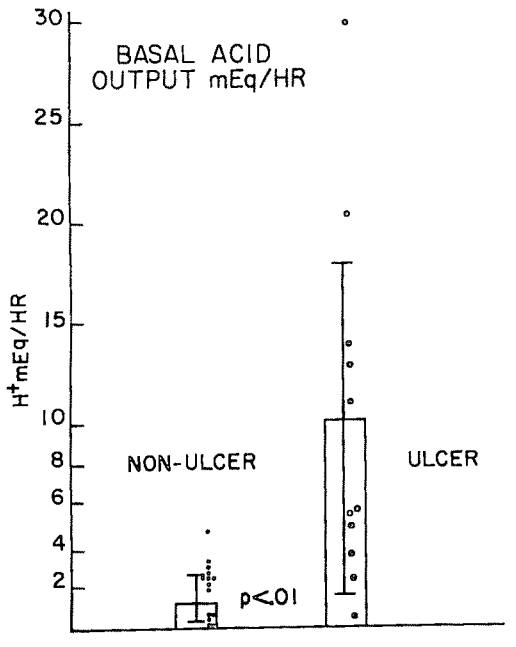


Fig. 1—Basal acid output (BAO) in mEq./H+/hr. in nonulcer vs. acute ulcer patients.

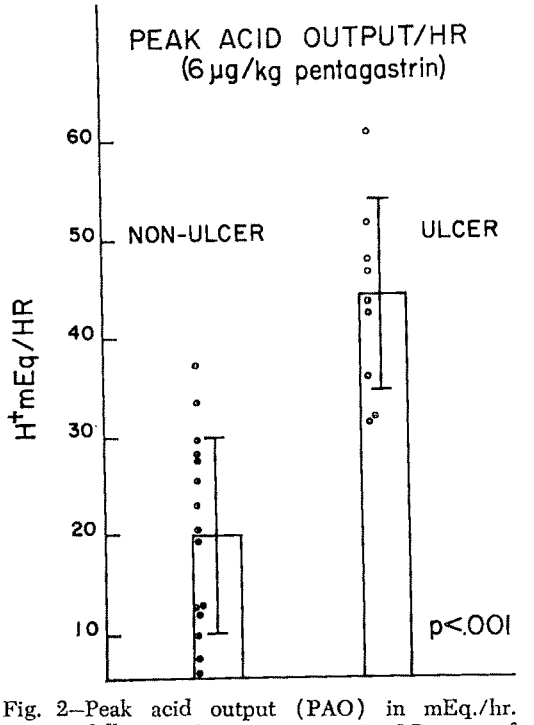


Fig. 2—Peak acid output (PAO) in mEq./hr. following 6 µg. pentagastrin SC; sum of two highest consecutive 15 minute specimens × 2.

umes of each specimen were recorded and all studies were done on unfiltered juice. The hydrogen ion concentration of each specimen was determined by titration to pH of 7.0 against a pH meter with 0.1 N NaOH. Total hydrogen ion secretion (H^+) per hour was calculated in the basal hour (BAO); peak acid output/hr. (PAO) was calculated from the sum of the two highest consecutive 15-minute specimens times 2.

Pepsin concentration[6] was determined in a 1:10 dilution of each specimen by meas-

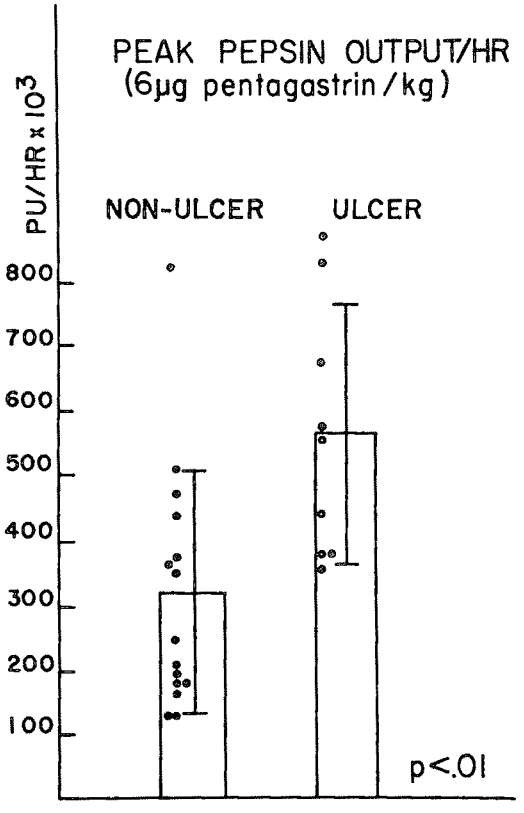


Fig. 3—Peak pepsin output (PPO) in pU./hr. × 10^3 following 6 μg. pentagastrin SC; sum of two highest consecutive 15 minute specimens × 2.

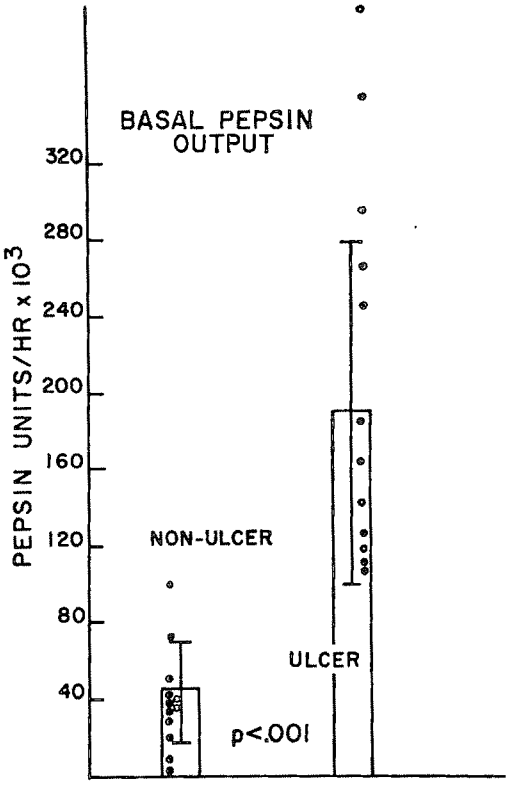


Fig. 4—Basal pepsin output (BPO) in pU./hr. × 10^3 in non-ulcer patients vs. acute ulcer patients. Open circles represent the three patients with acute gastric ulcer.

uring the rate of hydrolysis of denatured hemoglobin at 280 mm. and expressed as pepsin units/hr. (pU./hr.) in the basal hour (BPO); peak pepsin output (PPO) was calculated from the sum of the two highest consecutive 15-minute specimens times 2.

Results

In this study, both the basal and pentagastrin stimulated acid and pepsin outputs in the nonulcer group were significantly lower ($P < .01$) than in the acute ulcer group (Table I). There was appreciable overlap, however, in the two groups in BAO, PAO, and PPO (Figs. 1, 2 and 3) so that their calculated sensitivities were poor.

In the case of BPO, there was no overlap of values (Fig. 4) and no patient in this preliminary study had a basal pepsin output of more than 100,000 pU./hr. unless an ulcer was present. The calculated sensitivity of BPO was 100%; specificity, 93%. If one defines a "positive" BPO test as greater than two standard deviations above the mean value of 44.47 × 10^3, then the posttest risk of any single patient having an acute ulcer is 0.91 using Rifkin and Hood's formula for Bayes Theorem.[7] By contrast, the calculated posttest risk using PPO is 0.75, BAO 0.88, and PAO 0.33.

There was approximately a three-fold difference in BAO/PAO and BPO/PPO in both groups (Table II).

TABLE II

COMPARISON OF BASAL/STIMULATED RATIOS OF THE MEANS IN NONULCER VS. ACUTE ULCER PATIENTS

	Nonulcer	Ulcer
BAO/PAO	8.2%	22.4%
BPO/PPO	14.1%	34.2%

COMMENT

There are sufficient data available to indicate that gastric pepsin is critical to peptic ulcer disease.[8-10] Hydrochloric acid secretion, about which we have an astounding mass of data, is equally critical but may serve primarily to establish the appropriate milieu for peptic activity. While it may remain true that measuring HCl, because of its simplicity and well-investigated response to stimuli and inhibitors, will continue to give us useful clinical data, it will, of necessity, be incomplete information.

These studies will need to be extended to considerably greater numbers of patients before meaningful data are accumulated. The symptomatic patients in the nonulcer group do not make up a homogeneous population but may be defended on clinical grounds since peptic ulcer disease had been included in their differential diagnosis at some point in their immediate illness. The lack of over-lap in basal pepsin output between the two groups was unexpected and it remains to be seen whether or not this is a reliable differentiation as more patients are studied. To date we have not adequately studied patients with proven peptic ulcer disease in remission. Our first impression, however, is that quantitative determination of gastric pepsin secretion in these patients are not appreciably or consistently different from controls. These studies are underway.

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Prostaglandin E_1 Inhibition of Acid but Not Gastrin

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Prostaglandin E_1, while inhibiting gastric fistula and Heidenhain pouch acid output in the dog, did not inhibit gastrin released by acetylcholine irrigation of an isolated antral pouch independent of pH effect. Some increase in gastrin was noted to PGE_1 against a background of calcium infusion and following a meal. This increase is presumably due to acid inhibition and to an increase in intraluminal pH.

Introduction

Previous studies have documented that Prostaglandin E_1 (PGE_1) inhibits gastric acid secretion in animals and in man.[1-4] Becker, et al have previously demonstrated acid inhibition by I.V. PGE_1 after a meal despite an increased gastrin response.[5] Yet, gastrin inhibition by PGE_1 might have been masked by the reduction of intraluminal acid thus eliminating antral inhibition by acid. Ingested 16, 16 Dimethyl PGE_2 seems to inhibit gastrin release in patients perhaps by a topical effect.[6] In an attempt to evaluate these possible mechanisms, the effect of PGE_1 on the gastrin response to a meal and to acetylcholine release of gastrin from the isolated antrum independent of pH effect was studied.

Methods

Two mongrel dogs were prepared with Heidenhain pouches (HP) and two others with gastric fistulas (GF), all with an isolated but innervated antrum exteriorized onto the abdominal wall. Gastrointestinal continuity was re-established by a gastroduodenostomy. Gastrin responses to a meal were studied in four additional mongrel dogs with only Heidenhain pouches. A three-week recovery period was allowed for all dogs and four-day intervals between every test. Antral pH was consistently 5.0-7.0.

Feeding and calcium responses:—Four dogs with a HP were sampled for gastrin levels with blood drawn just before eating and hourly for six hours following a standard meat meal. Dogs ate to satiety (300-900 gm.). Hourly serum gastrin was also measured for four hours during a standard calcium infusion (20 mg./kg./hr.). Gastrin data are reported as integrated gastrin output in picrogram-mins./cc. Five such base line feeding responses and three such base line calcium infusions without PGE_1 were performed in each dog. In test situations, PGE_1 (courtesy, Dr. J. Pike, Upjohn) was infused one-half hour prior to either calcium infusion or feeding and continued for one half of the period (two hours for calcium infusion, three hours for feeding response). Doses of PGE_1 studied were 0.25 μg./kg./min., 0.5 μg./kg./min., 1.0 μg./kg./min., 1.5 μg./kg./min. and 2.0 μg./kg./min. All infusions were performed at least 2-3 times in each dog for each dose.

Acetylcholine responses:—In another four dogs, after a 30-minute basal period during which the GF and HP acid output

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TABLE I

GASTRIN EFFECT OF PGE_1 ALONE

	Basal	.5	1.0
G	18	35	93 $P < .05$
030	6	38 $P < .05$	18
075	41	10	2.5
084	177	148	225

Mean basal gastrin levels (3-5 tests) in picograms/cc. Significance by paired "t" test compared to control.

and serum gastrin was determined, the exteriorized antral pouch was irrigated with 1% acetylcholine at pH 7.0. Gastric acid and serum gastrin were determined every 15 minutes for two hours. On test days, PGE_1 infusion was added during the first hour at 1 μg./kg./min. and was discontinued for the second hour. All testing was performed 3-5 times in each animal.

Gastrin was assayed by our standard radioimmunoassay using antibody to synthetic human gastrin I (Imperial Chemical Industries, Ltd.) produced in white New Zealand rabbits. Acid was titrated to pH 7.0 with 0.1 N/NaOH on an automatic titrator (radiometer). Integrated gastrin output for a two hour period during calcium infusion and a three-hour period after feeding was calculated and expressed in picogram-min./cc. Mean acid output for each hour and serum gastrin levels to acetylcholine stimulation were calculated. A paired "t" test was used for comparison and $P < .05$ taken as a significant difference.

RESULTS

Feeding and calcuim response:—PGE_1 infusion for 30 minutes alone had no consistent effect on basal gastrin levels with stimulation noted only in one of four dogs at each dose (.5 μg. and 1.0 μg./kg./min.)

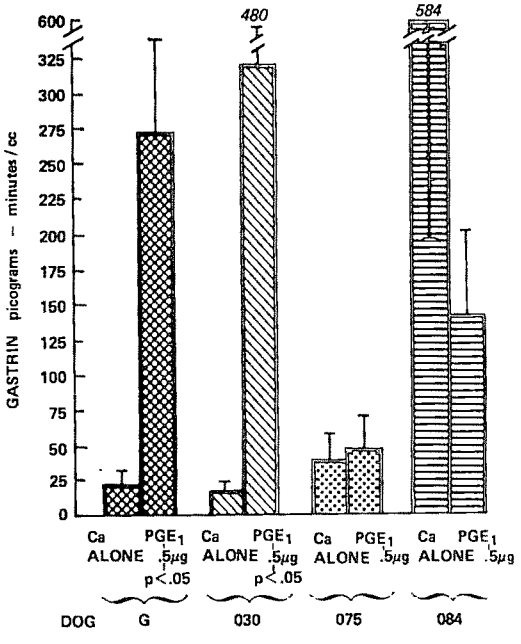


Fig. 1—Integrated gastrin output for two hours with calcium and calcium plus 0.5 μg./kg./min. PGE_1. Significance by paired "t" test. Individual dogs G, 030, 075, 084 compared.

level used (Table I). While calcium infusion alone did not stimulate gastrin release, PGE_1 at the .5 μg. dose level stimulated output in two of four dogs (Fig. 1). In response to a meal, PGE_1 infused at various doses did not inhibit gastrin response (Fig. 2). In two dogs, stimulation in gastrin release was demonstrated at 1.5 μg./kg./min. and at 1.0 μg./kg./min. as well in one dog.

Acetylcholine stimulation:—Acetylcholine irrigation of the antral pouch significantly stimulated gastrin output for the entire two-hour test period. No significant differences occurred between the first and second hour in any dog (Figs. 3 and 4). With the addition of PGE_1 infused at 1.0 μg./kg./min. during the first hour, no inhibition of gastrin was noted (Figs. 3 and 4). Acid output induced by antral irrigation with acetylcholine (Table II) was inhibited by PGE_1 in all four dogs but sig-

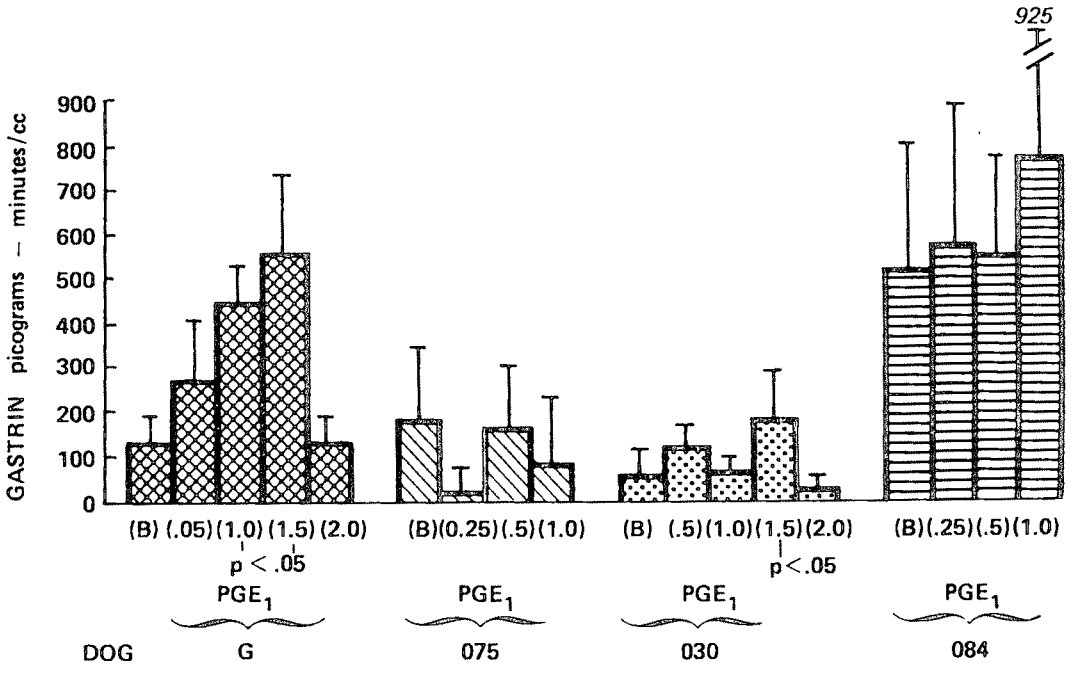


Fig. 2—Integrated gastrin output for three hours following a meat meal alone (B) and with a background of various doses of PGE_1. Significance by paired "t" test. Individual dogs G, 030, 075, 084 compared.

nificantly in ¾. The one dog in which a statistically significant inhibition was not achieved was one in which an HP was tested.

Comment

Prostaglandin and in particular, PGE_1, has been shown to inhibit acid output to a variety of stimuli in the rat,[4] dog[2, 3] and man.[1] The mechanism of its inhibition is theoretical but may include effects on mucosal blood flow, inhibition of gastrin, or a direct parietal cell effect, perhaps via cyclic AMP (cAMP).

In our study, acid, stimulated primarily by gastrin released by acetylcholine irrigation of the isolated antrum, was inhibited by PGE_1 without inhibiting the increased gastrin release. The only previous study assessing the effect of parenteral PGE_1 on gastrin was that of Becker, et al studying the effect following a meal.[5] Significant elevation of gastrin was noted in response to a meal despite concomitant inhibition of acid by PGE_1 infusion. This elevation was attributed by them to increased intraluminal pH.[5] This pH effect, thus may counteract and thus mask any inhibition of gastrin that PGE_1 otherwise might cause. Our study also confirmed some degree of increased gastrin response to a meal by PGE_1 but without a real effect on basal output. No effect on gastrin levels stimulated by antral irrigation with acetylcholine was noticed. This would confirm that PGE_1 does not inhibit either basal or stimulated gastrin release and increases noted following a meal are most likely secondary to increased intraluminal pH. Prostaglandin may have a direct topical effect on the antral G-cell since inhibition with oral 16, 16 Dimethyl PGE_2 has been demonstrated in patients fed a meal along with acid inhibition.[6, 7]

TABLE II

	Acetylcholine			ACH + PGE_1 Acethylcholine		
Dog	Hour 1	Hour 2		Hour 1	Hour 2	
R	.062	.096	NS	.042	.063	NS
CS	.008	.011	NS	.006	.017	$P < .05$
S	2.921	2.980	NS	3.659	5.951	$P < .05$
MM	1.034	.884	NS	.111	.934	$P < .05$

Mean total acid output for one hour in mEq. for 3-5 tests. Dogs R and CS with HP and Dogs S and MM with GF. The first hour with and without PGE_1 are compared to the second hour by paired "t" test.

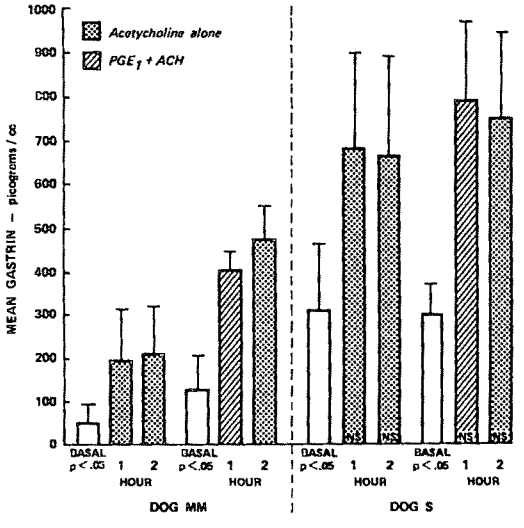


Fig. 3–Mean gastrin levels in two dogs sampled every 15 minutes. PGE_1 infusion is added to first hour of acetylcholine pouch irrigation on test dogs. $P < .05$ indicates significantly lower basal gastrin compared to both hours of ACH stimulation. Hours 1 and 2 were "NS" compared to each other. S.E. indicated.

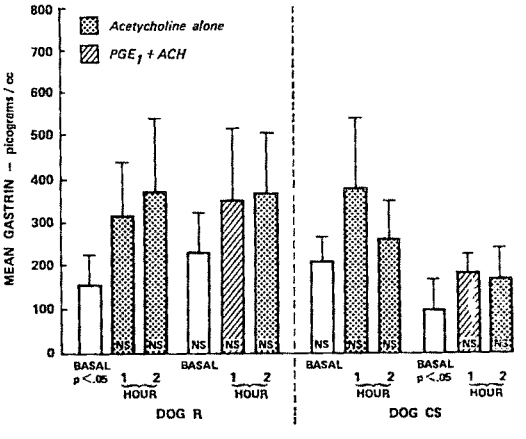


Fig. 4–Mean gastrin level in two dogs sampled every 15 minutes. PGE_1 infusion is added to first hour of acetylcholine pouch irrigation on test dogs. Basal ($P < .05$) indicates significantly lower basal gastrin compared to both hours of ACH stimulation except where noted 'NS". Hours 1 and 2 were NS compared to each other. S.E. indicated.

Increased gastrin output by PGE_1 against a background of calcium infusion occurred in two out of four dogs. Since this was not consistently evident in all dogs, its significance is in doubt but may represent a synergistic effect by Ca and PGE_1 on cAMP which may be required for antral and duodenal gastrin release.[8]

Although PGE_1 decreases gastric mucosal blood flow[4, 9, 10] such decrease has been shown not to be related to its inhibiting effect on gastric acid secretion.[9] It would seem that PGE_1 may have a direct cellular effect and this has been confirmed in *in vitro* preparations.[11] Although cAMP has a definite role in stimulating acid output in some species (i.e. frog, rat, rabbit),[12, 13] its role in dog and man is less clear.[14, 15]

PGE_1 has been shown to stimulate the cAMP formation and adenyl cyclase activity in many systems.[16] Increased cAMP has also been correlated with gastrin release in the guinea pig[8] and definite elevation in basal gastrin was noted in this study. While some have demonstrated that initiation of acid secretion in dogs does not depend on accumulation of cAMP,[15] others have demonstrated, in the frog, increased acid and cAMP induced by pentagastrin, this response blocked by PGE_1.[11, 17]

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Complications of Vagotomy

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Most operations performed for peptic ulcer disease in the United States include vagotomy as part of the surgical procedure. This paper reviews the complications associated specifically with or increased in frequency and severity by this procedure.

Included in this review are technical complications, gastric retention, recurrent ulceration, postvagotomy diarrhea, postvagotomy dysphagia and achalasia, postvagotomy biliary disease and nutritional problems. The frequency of these complications, their pathophysiology and therapeutic modalities available are reviewed. The main emphasis is on postvagotomy syndrome that can be treated medically and on the various treatment forms that have been suggested.

The aim of surgery for duodenal ulcer is to cure the ulcer with a minimum of side-effects. This is accomplished by performing an operation that will: 1. reduce gastric acidity and 2. keep the gastrointestinal tract as close to normal as possible. Gastric surgery has evolved over the years toward this aim. Subtotal gastrectomy with Billroth II anastomosis was the main operation for ulcer up to the 1960's. Several less crippling procedures have been devised in an effort to decrease the incidence of postoperative complications. These procedures are vagotomy and hemigastrectomy or antrectomy, vagotomy and pyloroplasty, vagotomy and gastrojejunostomy, selective vagotomy and drainage and highly selective (parietal cell) vagotomy without drainage. Most of the operations performed for the treatment of peptic ulcer include some type of vagotomy. We review the complications that have been particularly associated or more frequently associated with this procedure.

Technical Complications

These probably concern the surgeon more, since they become evident during surgery or soon thereafter.[1] Splenic rupture occurs in about 3% of patients, esophageal perforation in less than 1% of patients; esophageal mediastinal hemorrhage and esophageal devascularization have also been reported.[2] The vena cava may be injured during mobilization of the esophagus and left hepatic infarction can occur as a result of mobilization of the liver in an effort to find the vagus nerve.[1] Treatment is usually surgical.

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Gastric Retention and Vomiting

This is usually an early complication. The most common cause is an inadequate drainage procedure in the face of decreased motility of the stomach caused by the vagotomy. This complication is less likely to occur after highly selective vagotomy because antral peristalsis is preserved and drainage procedures are not required.

Gastric retention is treated by nasogastric suction and slow resumption of feeding. If persistent this complication may require surgical revision after appropriate studies prove that outlet obstruction is present.[4] Medical treatment includes bethanecol chloride (Urecholin), which has been useful when there is no mechanical obstruction.[5, 6] Metaclopramide, at present an investigational drug in the United States is promising in the medical treatment of this complication.[7]

Recurrent Ulceration

The following is the reported incidence of recurrent ulcer after various surgical procedures for treatment of duodenal ulcer: vagotomy and hemigastrectomy less than 1% (0.5%), resection alone 2-5% (3.7%), vagotomy and pyloroplasty 4-25% (8.9%), vagotomy and gastroenterostomy 5-10% (5.7%). The figures in parenthesis are taken from the Veterans Administration cooperative study.[8] The incidence of recurrent ulceration after highly selective vagotomy has not been established yet because of the newness of the procedure. In a cooperative study,[9] duodenal ulcer was suspected in 3% of patients, it was proven in none but two patients had gastric ulceration after surgery. In another report[10] the incidence of recurrent ulceration was 22%. This discrepancy might be caused by a difference in technic.

The completeness of vagotomy can be estimated by gastric analysis. The correlation, however, between the response to insulin stimulation for acid (Hollander test) and recurrent ulceration after surgery is poor and insulin stimulation may be no better than other tests of acid secretion in separating patients with recurrent ulceration from those without ulceration after vagotomy.[11] Upper gastrointestinal endoscopy is the best method available for diagnosis of ulceration after surgery and is superior to roentgenology in this respect.[12]

The main cause of postvagotomy peptic ulceration is incomplete vagotomy. Other factors to be considered include inadequate gastric resection, retained gastric antrum (after Billroth II operation), Zollinger-Ellison syndrome, hypercalcemia and the administration of ulcerogenic drugs.[13]

The treatment of postsurgical ulcer is often surgical because of the poor response to standard medical therapy. The response to H_2 receptor antagonists has not been adequately studied.

Postvagotomy Diarrhea

Diarrhea is the most frequent complication of vagotomy. An increased frequency of bowel movements over what is normal for the individual occurs in up to 60% of patients; it is a significant symptom that requires treatment in about 5% of patients.[14]

The frequency of this complication was the reason for introducing bilateral selective vagotomy, sparing celiac and hepatic branches, in the hope that the motility of the small bowel and pancreatic function would be unaltered. Some studies find no difference in the incidence of diarrhea between truncal and selective vagotomy.[15] This suggests that the drainage procedure *per se* and dumping contribute in part to the problem of diarrhea as is further evidenced by the decreased frequency of this

complication after highly selective vagotomy without a drainage procedure.[16]

The mechanism of postvagotomy diarrhea has not been established. Dragstedt postulates for some cases bacterial overgrowth secondary to stasis in the small bowel and decreased acid secretion by the stomach.[14] Other proposed mechanisms include poor mixing with enzymes and loss of control of gastric emptying, as a result of which a solid meal does not increase colonic activity while a liquid meal is followed by greater colonic activity after vagotomy than in the control population.[17] Increased bile salt load to the colon because of dilatation of the gallbladder and deconjugation of bile salts due to bacterial overgrowth in the small intestine is responsible for the diarrhea in some cases.[18, 19]

In the evaluation of patients who develop diarrhea after vagotomy other possibilities have to be considered, in particular conditions that are amenable to specific therapy such as celiac sprue, lactase deficiency or bacterial overgrowth which may become apparent after surgery.[20]

The diet should be similar to the one recommended for treatment of dumping syndrome in an effort to reduce the increased colonic activity and diarrhea that follow a liquid load. This diet should consist of frequent solid feedings, high in protein and low in carbohydrates and fat. Liquids should be given in small amounts preferably only with meals and milk should be avoided since it often causes diarrhea *per se*. In more severe cases anticholinergics and diphenoxilate (Lomotil®) might be added. Bethanecol has been used and possibly improves symptoms by increasing the tone of the bowel.[21]

Several patients with postvagotomy diarrhea presumably secondary to increased bile salt load to the colon have responded to treatment with cholestyramine.[18, 19] In severe cases that are not controlled by the previous measures nasogastric suction for a few days, followed by frequent feeding with a slow increase in volume has been recommended and is occasionally successful.

Surgery is reserved for the unusual cases of incapacitating diarrhea that do not respond to any of the above medical manuevers. These comprise, at most, 0.3% of all patients undergoing vagotomy. The surgical procedure that has been proposed is to interpose a reverse jejunal segment 10 cm. in length, 50-100 cm. distal to the ligament of Treitz causing an antiperistaltic loop of small intestine. This has performed well in several patients and suggests that hypermotility of the bowel is one of the mechanisms in this complication.[22, 23]

Postvagotomy Dysphagia and Achalasia

This complication was first reported in 1947 by Moses.[24] It has been studied since in detail.[2, 24, 31] Dysphagia presents within the first two weeks after surgery, soon after the first solid food is given. Substernal distress is common and in most cases not severe and often the dysphagia lasts three to four weeks and remits spontaneously. The incidence varies from 0-27% of patients. By manometric studies of the esophagus the patients have been divided into two groups. The first group has been noted to have lack of relaxation of the gastroesophageal junction with swallowing and sometimes atony of the distal esophagus. Barium studies demonstrate smooth distal esophageal narrowing (postvagotomy achalasia). The second group of patients have relaxation of the sphincter after swallowing and a normal or increased tone of the esophageal musculature. In this group, dysphagia is attributed to periesophageal and esophageal edema and is frequently pain-

ful. Radiographically there is narrowing of the distal 4-5 cm. of esophagus with proximal dilatation.[26, 31] At esophagoscopy the usual finding is enlarged edematous folds.[29]

In those cases that do not remit spontaneously, esophageal dilation with a mercury bougie is recommended and usually few sessions are required for improvement of symptoms. This form of therapy is more frequently necessary in patients with a long narrow segment and mucosal edema.[2, 29] Other rare esophageal complications have been described such as periesophageal fibrosis requiring repeated dilation or even surgery in some patients.[29] In one instance of dysphagia a foreign body granuloma was found in the cut-end of the vagus nerve suture causing obstruction of the esophagus.[27]

Hiatal hernia is reported after vagotomy in up 10-15% of patients, it might be associated with esophageal reflux and cause symptoms of esophagitis on this basis.[2]

Postvagotomy Gallbladder Disease

Vagal excitation produces contractions of the stomach, small bowel and ascending colon and maintains tone of the gallbladder, therefore vagotomy may result in visceral atony. Dilatation and decreased contraction of the gallbladder has been demonstrated in several studies within a year after vagotomy.[32, 33] This disturbance is probably temporary.[34] Whether vagotomy increases the incidence of gallstones is controversial, there are clinical and experimental data in support as well as against this concept. The available information has been summarized by Bouchier.[35] The prospective duodenal ulcer study of the Veterans Administration[1] did not demonstrate a difference in the incidence of gallstones in patients with and without vagotomy.

Nutritional Problems Associated with Vagotomy

The late nutritional complications of vagotomy alone are very difficult to assess because gastric resection or drainage procedures are usually done together with truncal and selective vagotomy.

Patients studied 15-20 years after surgery had lower serum folate following only vagotomy than after resection alone. Both groups had similar weight loss. The hemoglobin, serum B_{12} levels and bone density were more abnormal in the gastrectomized patients.[36] Of 192 patients seen at least 10 years after vagotomy and pyloroplasty or gastrojejunostomy,[37] a majority were below the average weight for height, sex and age and there was no difference between pyloroplasty and gastrojejunostomy; serum iron was significantly lower after gastrojejunostomy than after pyloroplasty. The serum calcium was lower after gastrojejunostomy in men and lower after pyloroplasty in women. Among 255 patients investigated 15 years after vagotomy and gastroenterostomy,[38] a significant number were below their standard body weights because of poor dietary intake caused by gastrointestinal symptoms. Forty-three and five tenths per cent were anemic, all had iron deficiency and low gastric acid output; no patient had osteomalacia, two had low serum calcium levels and there was a 7% incidence of tuberculosis. These reports suggest that iron deficiency may be specifically related to vagotomy; this will be further clarified in the long-term follow-up of patients after highly selective vagotomy.

In patients studied at least one year after surgery, steatorrhea was more prevalent after truncal vagotomy and pyloroplasty than after selective vagotomy and pyloroplasty or highly selective vagotomy.[39] The authors speculate that total gastric vagotomy and drainage lead to loss of control of

gastric emptying and subsequent rapid intestinal transit and poor mixing, in addition to decreased pancreatic secretion, resulting in steatorrhea. Most of these problems are eliminated by parietal cell vagotomy which therefore should be followed by fewer long-term nutritional problems.

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Clinical Value of Liver Scans*

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The contribution of technetium sulfacolloid liver scans on patient care was evaluated in 200 consecutive patients; 100 in a public (Grady) and 100 in a private (Emory University) hospital. The problem oriented record clearly described the effect of liver scan on: 1. *assessment* of the patient's problem(s) and 2. *plans* made for its diagnosis or management. For the diagnosis and treatment of 30 patients with intrinsic hepatobiliary diseases, the scan was useful in five but was misleading in four. Specific diagnosis was obtained by other methods which made the liver scan an unnecessary overutilization of a diagnostic procedure in the evaluation of patients with primary liver or biliary diseases. The scan was useful in 95 of 123 patients with extrahepatic malignancy. This was mostly due to chemotherapy protocols requiring the scans. Only 18% of positive scans had no other clinical evidence for hepatic malignancy. Definite diagnosis was not made in any of the 123 patients by liver scan. In 47 miscellaneous conditions the scan was useless in 37 (79%). In three of these the scan was misleading and impaired patient care.

The increasing use of sophisticated and expensive diagnostic procedures warrants review of their usefulness. The problem oriented record permits the evaluation of how a diagnostic procedure affected the care of a patient. To evaluate how liver scans affected the diagnosis and management of patients, 200 unselected scans were reviewed and are the subject of this report.

Methods

Two hundred consecutive patients, who had technetium sulfacolloid liver scans, were studied. One hundred were from Emory University Hospital and 100 from Grady Memorial Hospital. In the former institution, the patients were from the private sector and were under the direct care of a senior faculty person; in the latter, the patients were from the public sector and were under the direct care of house staff, supervised by a senior faculty person. In both hospitals, the problem oriented record had been in use and daily progress notes were recorded under the headings of S/O/A/P (Subjective and Objective data, Assessment of the data and the Plans based on the assessment). When the diagnosis or management of the patient was affected by a procedure or test, it was always recorded; its meaning was assessed and, when appropriate, plans were formulated on that basis. When the information obtained did not improve the understanding of the patient's problem, then either

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TABLE I

CLINICAL VALUE OF LIVER SCAN IN 200 CONSECUTIVE PATIENTS

	Total	Useful	Useless	Misleading
Malignancy	123	95 (77%)	28 (23%)	3 (2.5%)
Liver disease	26	5 (19%)	21 (81%)	4 (15%)
Cholestasis	4	0	4 (100%)	0
Miscellaneous*	47	10 (21%)	37 (79%)	3 (6%)

the assessment indicated that the test or procedure provided no additional information or the data became superfluous and was ignored altogether. Therefore, the understanding of the problem did not improve and no plans were formulated as the result of the test or procedure.

The results of liver scans were classified as: 1. diagnosis was correct; 2. diagnosis was incorrect; 3. indeterminate. When the diagnosis was correct, it either contributed to or established the diagnosis and affected the management of the patient (*useful*) or it was ignored (*useless*). When the scan diagnosis was incorrect it was either ignored or it was misleading (the diagnosis was not only incorrect but it led to other unnecessary procedures and resulted in additional risks, discomfort, expense and delays).

Liver scan provided a definite diagnosis when no additional procedures were required to establish the diagnosis; it contributed to the diagnosis when the procedure which established the diagnosis would not have been performed without the information provided by the liver scan as indicated by the initial plans. The liver scan was considered useless if the diagnosis made by the scan was not definite, it was already suspected before the scan and the additional procedure(s) which was (were) required to establish the definite diagnosis would have been performed without the liver scan diagnosis as indicated by plans recorded before the scan diagnosis.*

RESULTS

The distribution of liver scan results from the two different types of hospitals were similar. Therefore, the results were combined and reported together (Table I).

In no patient was a definite diagnosis made by liver scan. The final diagnosis was established by biopsy in 64 patients, by surgery in 82 patients, by autopsy in four patients (Table II), by endoscopy or x-rays in 17 patients (Table III) and by the clinical course in 33 patients (Table IV). During the follow-up period 74 patients died. Autopsy was performed in 17 which confirmed the previous "final" diagnosis in 13 and established it in four.

Among the 123 malignancies, 108 were sufficiently differentiated to be diagnosable: 86 were various types of carcinomas, 12 were lymphoma or leukemia, five were sarcomas, five melanomas and 15 were undifferentiated hepatic metastases from unknown

* For example: 1. If clinically chronic hepatitis or cirrhosis was suspected and the scan was compatible with chronic liver disease, the liver biopsy which established the diagnosis would have been done anyway, therefore, the scan was superfluous. 2. If the clinical diagnosis was chronic liver disease and the scan showed filling defects suggesting cancer and the biopsy diagnosis and the clinical course was that of chronic hepatitis, the scan was incorrect.

TABLE II

MISCELLANEOUS

Final diagnosis	Number of patients
Upper gastrointestinal bleed, unknown origin	1
Cholecystitis	1
Eventration of diaphragm	1
Tuberculosis	1
Weight loss	1
Stress erythrocytosis	1
Abdominal pain	4
Abdominal trauma	1
Transient ↑ SGOT (*minimal*)	1
Fever unknown origin	1
Aspiration	1
ASCVD	3
Acute pancreatitis	2
Anorexia nervosa	1
Functional gastrointestinal symptoms	2
Radiation proctitis	1
Polymyositis	1
Urinary tract infection	1
Cytomegalovirus	2
Anemia	3
ITP	3
Reflux esophagitis	2
Scapular pains	1
Depression	1
Chronic diarrhea	1
Congestive heart failure	2
Rheumatoid arthritis	1
Ulcerative colitis	1
Zollinger-Ellison syndrome	1
Liver abscess	2
Portal vein thrombosis	2
Total	47

sources. In this group the scan showed space-occupying lesions in 33, it was normal in 81 and was indeterminate in nine. In the 33 patients with positive scan the liver was enlarged in 14 (42%), the alkaline phosphatase (with or without SGOT) was elevated in 21 (64%). Only in six (18%) patients was the scan positive when neither hepatomegaly nor abnormal liver tests were detected.

The 26 patients with intrinsic liver diseases included 11 with cirrhosis, 11 with alcoholic hepatitis, two with viral and one with granulomatous hepatitis and one with fatty liver.

Only five of the 17 correct diagnoses directed plans for the appropriate diagnostic procedure. At the same time, in four patients the scan directed plans for unnecessary, expensive and invasive procedures and delayed the diagnosis.

The four patients with cholestasis had common bile duct obstruction. In three the scans showed no liver disease and were correct. One, however, suggested chronic liver disease. It was incorrect but it was ignored.

Two patients had abscesses. In one the scan correctly identified a filling defect and directed plans for a specific diagnostic test but it missed the abscess in the second patient.

Two patients had portal vein thrombosis with variceal bleeding. In both, the liver scan demonstrated normal liver and enlarged spleen with no shift of the radionucleide to bone marrow. Therefore, it was helpful to direct attention away from cirrhosis and to portal or splenic vein thrombosis. The scan was not diagnostic and angiography was needed to establish a final diagnosis.

In the remaining 43 patients the liver scan was normal and correct in 34. It was useful only in seven of these 34 scans (20%). The remaining nine scans were abnormal; six were ignored but three of these nine were misleading.

COMMENT

We found no justification for the routine use of liver scan in patients with

TABLE III

FINAL DIAGNOSIS MADE BY X-RAY OR ENDOSCOPY

Diagnosis	No.	Diagnosis	No.
Bone x-rays	8	Metastatic CA (prostate)	7
		Metastatic CA (breast)	1
Angiography	3	Amebic abscess	1
		Portal vein thrombosis	2
Chest x-ray	2	Pneumonia	1
		Eventration of diaphragm	1
Cholecystography	1	Cholelithiasis	1
Barium enema	1	Radiation colitis	1
Endoscopy	2	Reflux esophagitis	2

hepatobiliary disease. In this group others reported that the liver scan can be misinterpreted[1-8] and in our study, the scan was misleading and harmful almost as often as it was helpful. Although in five of the 30 patients with hepatobiliary diseases the scan was useful, they could have been adequately and efficiently diagnosed just as well without the scan.

For the diagnosis of hepatobiliary disease, liver scan should not be ordered when specific diagnosis can be obtained by another procedure. Those procedures which give suggestive or collaborative information should be omitted when definite diagnosis can be obtained by another procedure. The definitive test should be performed first instead of last.

The diagnostic accuracy of liver scans was impaired by false-positive[9-16] and false-negative[10-14, 17, 18] results. The reported diagnostic accuracy of the liver scans depended on the selection of patients. For example, when the purpose of the liver scan was to identify cancer in liver without other disease, the reported diagnostic accuracy of the scan was high.[19-21] Accordingly, the scan was considered useful in two-thirds of 123 such patients in our study. When, however, we classified the scan diagnosis as useful, it was an overstatement. As was observed by others[22] the vast majority of patients with positive scans were suspected to have hepatic malignancy because of hepatomegaly or abnormal liver tests. In our study, the usefulness of the scan in this group was largely because the oncology service used liver scan as part of the chemotherapy protocol. How many of these so-called useful scans had direct usefulness for patient care is a matter of conjecture, since chemotherapy was given by protocol and clinical response was evaluated only after completion of treatment. For diagnosis of cancer, tissue diagnosis is essential and scan defect is not sufficient. Therefore, when cancer of the liver is suspected, a liver biopsy (blind or through peritoneoscopy) is needed. When objective evidence is required for the evaluation of cancer chemotherapy administered by protocol, then liver scan can become useful.

It was anticipated that the utilization of diagnostic procedures, such as a liver scan, was done with greater discernment by seasoned physicians than by house officers. The lack of a statistically significant difference in the utilization of liver scans on private and public patients suggested that the selection of diagnostic procedures by

TABLE IV

FINAL DIAGNOSIS MADE BY CLINICAL METHODS

Diagnosis	No.
Alcoholic hepatitis*	10
Psychosomatic illness	8
Cardiovascular diseases	4
Hematologic diseases ITP, anemias stress erythrocytosis	6
Miscellaneous cholecystitis urinary tract infection FUO Rheumatoid arthritis transient ↑ SGOT	5

* With or without cirrhosis—biopsy was not done because of prolonged prothrombin time.

our housestaff was affected by the mature judgment of senior faculty or vice versa. At any rate, the similarity of results obtained in two very different types of hospitals suggested that our experience with the overutilization of liver scans was probably representative of nonacademic hospitals.

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First 24 Hours of Acute Pancreatitis

A Biochemical and Endocrine Evaluation of Initial Versus Repeated Attacks

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Differences in metabolic homeostasis in 12 patients with initial vs. eight patients with repeated attacks of acute pancreatitis have been compared during the acute phase of the disease. As a group, subjects with a previous history of pancreatitis had significantly lower glucagon concentrations ($P < 0.002$) for the over all 24-hour study period. Conversely, the serum concentrations of blood sugar, insulin, growth hormone, gastrin, cortisol, nonesterified fatty acids, triglycerides and cholesterol failed to distinguish between the two patient groups. Likewise, immunoreactive plasma parathyroid hormone and calcitonin levels were comparable in both patient populations. Of the measurements considered, it would appear therefore that plasma immunoreactive glucagon is the best indicator of previous pancreatic inflammation. Evaluation of parenchymal integrity during an episode of acute pancreatitis would be of prognostic and therapeutic value in this disease.

Changes in biochemical and endocrine homeostasis commonly accompany an attack of acute pancreatitis (AP). Both the inflammatory process involving the pancreas as well as the stress imposed by the disease itself contribute to the metabolic fluctuations observed.[1] Certain endocrine responses, however, not accounted for by stress alone, are associated with AP. One such example is the striking elevation in plasma glucagon levels observed in the acute phase of the disease.[1, 2] Furthermore, by comparing patients with an initial attack of AP versus those experiencing a recurrent episode, diminished plasma glucagon concentrations have been noted in the latter patient group.[3] Indeed, plasma glucagon levels have been proposed as an index of

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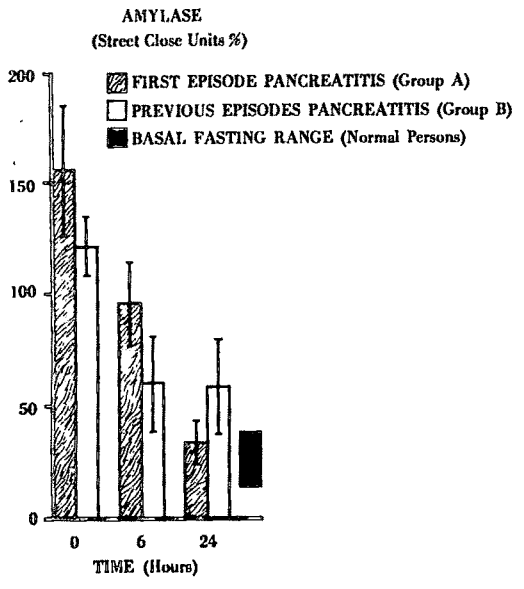


Fig. 1—Serum amylase levels (mean ± 1 SEM) in Group A and Group B pancreatitis patients.

pancreatic injury in patients with a history of previous pancreatitis.[3] In the present report we have studied additional select biochemical and endocrine responses during the first 24 hours of AP, placing a special emphasis on differences in patients experiencing a first attack as opposed to those with a previous history of acute pancreatic inflammation. The dichotomy of hormonal responses observed in these two subgroups of pancreatitis patients is discussed in relation to the metabolic abnormalities which characterize chronic pancreatic inflammation.

Patients and Methods

Pancreatitis populations:—20 successive patients with AP were evaluated. The diagnosis of AP was established by elevated serum and urine[4] amylase values (17 patients) and evidence of pancreatitis at laparotomy (three cases). The patient population was divisable into two groups: *Group A*, 12 patients, 11 males and one female, with no previous history of AP, and *Group B*, comprising eight patients, seven males and one female, with one or more previous episodes of AP requiring hospitalization. Of the eight patients, five had a history of one previous attack and two patients had been previously hospitalized with AP on two and three occasions, respectively. The mean ages of the respective patient populations was 37 ± 2 years (range 24-51) for Group A and 34 ± 1 year (range 29-42) for Group B. The etiology of the pancreatitis was chronic alcoholism in 18 of the cases and biliary (Group A) and idiopathic (Group B) pancreatitis in two cases, respectively. No subject in either of the groups had any clinical evidence of chronic pancreatitis, malabsorbtion or pancreatic calcification. None had a known history of diabetes or hyperlipidemia and the two female patients were not on any form of oral contraception.[5] One patient presented in oligemic shock (Group A) and one other patient (Group A) with pancreatitis and cholelithiasis was mildly jaundiced on admission. Renal function as determined by blood urea nitrogen and serum creatinine levels was normal in all but one patient (Group A). None of the patients had evidence of cirrhosis. All patients were within 20% of their ideal body weight. The delay following the onset of clinical symptoms to the time of hospitalization was 36 ± 7 hours for Group A and 38 ± 6 hours for Group B patients.

In all cases the initial 24-hour treatment protocol included intravenous fluid therapy, antimuscarinics (propantheline), nonnarcotic analgesics, antibiotics (penicillin or ampicillin) and nasogastric suction. Serial serum samples were drawn from the patients immediately on admission and at six and 24 hours postadmission, with an attempt made to limit the use of a tourniquet. In the majority of the patients the first sample was obtained prior to the initiation of intravenous fluid therapy. As far as could be ascertained, none of the patients had

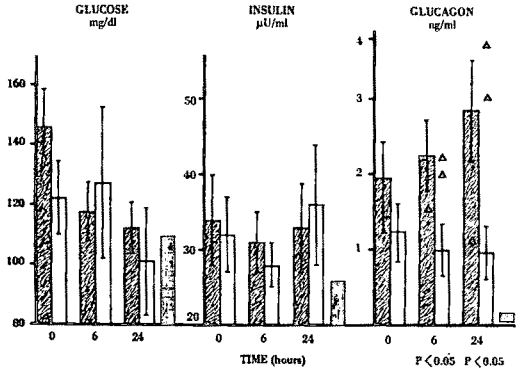


Fig. 2—Blood glucose, insulin and glucagon levels (mean ± 1 SEM) in Group A and Group B pancreatitis patients. Plasma glucagon concentrations (△) in patients receiving intravenous glucagon are excluded from the mean values shown.

taken food for 12 hours prior to admission. Six serum samples, two from Group A and four from Group B, were obtained from patients receiving intravenous glucagon therapy and these results have been excluded from the calculations. More than 75% of all blood samples in both patient groups were drawn during the course of glucose-free intravenous fluid administration. The remaining samples were obtained from subjects receiving a 5% invert sugar solution infused intravenously at the rate of approximately 125 ml. per hour. The duration of hospitalization for patient groups A and B was 8 ± 2.5 days and 8 ± 1.5 days, respectively. Excluded from the latter calculation are the one Group A and three Group B patients, whose period of hospitalization was extended as a result of the development of pancreatic pseudocysts and an additional Group A patient who died of AP 18 hours following admission to the hospital.

Laboratory assays:—Biochemical and endocrine measurements were determined by similar methods or modifications of the assays referred in the bibliography: blood glucose,[6] insulin,[7] glucagon,[8] growth hormone,[9] gastrin,[10] cortisol,[11] nonesterified fatty acids,[12] triglycerides[13] and cholesterol.[14] Plasma immunoreactive parathyroid hormone and calcitonin concentrations were kindly estimated by Dr. L. J. Deftos.[15, 16] Total serum calcium, magnesium, amylase and routine liver function tests were estimated by standard biochemical technics. The serum calcium values were corrected for the serum albumin concentration.[17] Basal fasting levels of the hormones and the range of biochemical values for normal individuals as determined in our laboratories appear in the text or accompany figures showing variations of these measurements in each of the patient populations.

The comparison of group data was performed using the Student "t" test and correlation coefficient analyses.[18] The study was conducted under the auspices of the Human Research Council of the University of the Witwatersrand and informed consent obtained from all participating patients and volunteers. Standard medication was administered to all patients as described above.

Results

Comparable serum amylase values occurred in both patient groups at each assay interval for the first 24 hours following admission (Fig. 1). Although blood glucose levels were elevated in Groups A and B (Fig. 2), the hyperglycemia failed to distinguish between the two patient populations. Considering, however, the first six hours of hospitalization, some evidence for a persistent hyperglycemic response in Group B patients was present, whereas blood glucose values in Group A subjects fell over the same time period. Serum insulin concentrations were raised above basal fasting levels in both pancreatitis groups (Fig. 2) although no significant differences in insulin levels were noted at each of the time intervals or for the over all 24-hour study period. Furthermore, a com-

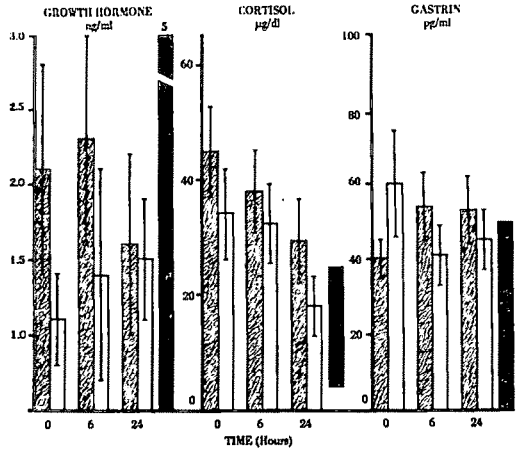


Fig. 3—Serum growth hormone, cortisol and gastrin levels (mean ± 1 SEM) in Group A and Group B pancreatitis patients.

parison of the glucose/insulin ratios between the two groups showed no evidence suggestive of a greater diminution in carbohydrate tolerance in patients with a previous history of pancreatitis. In both Group A and B patients, plasma-immunoreactive glucagon concentrations were raised above normal basal fasting values (Fig. 2). Glucagon levels in Group B patients, however, were significantly lower than Group A subjects both at six ($P < 0.05$) and 24 ($P < 0.05$) hours and for the over all 24-hour study period ($P < 0.002$). No correlation between blood glucose, insulin, or glucagon levels was established for either of the pancreatitis populations. Furthermore, no differences in the serum concentrations of glucose, insulin, or glucagon were present in patients receiving invert sugar versus sugar-free intravenous fluids.

A wide variation in serum growth hormone (GH) concentrations within the range of normal values (0-5 ng./ml.) occurred in both pancreatitis populations (Fig. 3). No significant differences were noted between the two patient groups, although the mean serum GH concentrations tended to be lower in Group B patients on admission and at six hours compared with their Group A counterparts. Serum cortisol levels were elevated in both groups, especially in the initial six hours following hospitalization (Fig. 3). Conversely, serum immunoreactive gastrin levels remained within range of the normal basal fasting values and comparable values were observed in both patient populations (Fig. 3). As regards the lipid profile in AP (Fig. 4), no differences were noted between the levels of serum cholesterol or triglycerides in Groups A and B and the blood concentrations remained within the normal basal fasting range. Serum nonesterified fatty acid (NEFA) concentrations were elevated in both groups A and B on admission. No significant differences, however, were present if NEFA concentrations in Group A patients were compared with levels observed in subjects experiencing a second or subsequent episode of acute pancreatitis.

In both patient groups total serum calcium (corrected) and magnesium concentrations remained within physiological limits (Fig. 5). Plasma-immunoreactive calcitonin concentrations were minimally elevated above the assay limit for normals (< 100 pg./ml.) in both Groups A and B subjects. A wide variation in parathyroid hormone (PTH) levels in response to AP occurred (Fig. 5). In two Group A subjects PTH values exceeded 20 ng./ml. and in a further two Group A and one Group B patients plasma PTH concentrations fell below the minimum detectable limit of the assay (< 0.15 ng./ml.). Considering all values, no significant differences were noted in PTH levels between Group A and B populations. No correlation between the serum concentrations of glucagon, calcitonin, parathyroid hormone and total serum calcium could be demonstrated in either patient group. In those subjects receiving exogenous glucagon therapy, no correlation

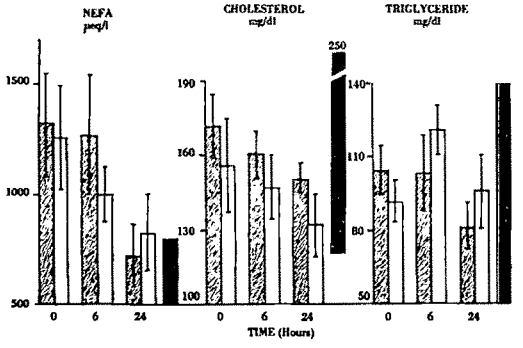


Fig. 4—Serum nonesterified fatty acids (NEFA), cholesterol and triglyceride levels (mean ± 1 SEM) in Group A and Group B pancreatitis patients.

was observed between plasma glucagon concentrations and PTH or calcitonin levels.

Comment

Abnormal metabolic homeostasis is a feature of both acute and chronic pancreatitis. The relation, however, of altered biochemical and endocrine response to the natural progression of pancreatic inflammation is inadequately defined. Early recognition of pancreatic insufficiency based on patterns of metabolic response during an episode of pancreatitis could have important prognostic and therapeutic implications. By comparing two groups of pancreatitis patients, one with a previous history of AP, we have sought to identify differences in metabolic response which may be attributed to the insiduous onset of parenchymal damage and manifest during the occurrence of a second or subsequent attack of acute pancreatitis.

Carbohydrate intolerance is a hallmark of end stage inflammatory destruction of pancreatic tissue. The inability to cope, however, with a standard glucose load may occur following a single attack of AP.[19] Indeed, in 2% of individuals, the first episode of AP may mark the onset of a persistent diabetic state.[20] In the absence of an exogenous glucose challenge, it would appear from the blood sugar values, that the hyperglycemia of AP is not a sensitive indicator of previous pancreatic inflammation, and fails to distinguish between Groups A and B patients.

Impaired stimulated serum insulin responses may follow an initial attack of AP[19] and are a feature of chronic pancreatitis.[21] Furthermore, serum insulin levels in AP are inappropriately low in relation to the prevailing hyperglycemia.[1] Although this observation has been attributed to islet cell damage,[2] serum insulin concentrations in patients with a previous history of AP were not more adversely compromised and failed to reveal differences suggestive of previous pancreatic damage.

Plasma immunoreactive glucagon concentrations, however, did appear to differentiate between patients with a previous history of AP and those subjects undergoing an initial episode of the disease. Similar observations by Dunowitz and associates[3] have led them to propose this measurement as an indicator of previous pancreatic inflammation. Raised levels of plasma glucagon in AP[1-3] have been attributed to islet cell stimulation by the ongoing inflammatory process.[2] Observations of impaired stimulated glucagon release in subjects with a previous history of AP, however, as well as the occurrence of hypoglucagonemia in a number of cases of chronic pancreatitis,[22, 23] supports evidence favoring irreversible alpha cell damage in pancreatitis. As such, plasma glucagon concentrations in AP may provide a sensitive index of pre-existing parenchymal damage. Furthermore, in severe hemmorhagic pancreatitis, hypoglucagonemia rather than elevated plasma glucagon concentrations has been reported.[2]

Impaired GH responses secondary to insulin induced hypoglycemia may occur

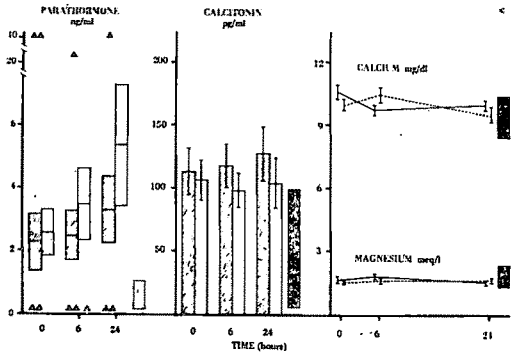


Fig. 5—Plasma parathyroid hormone (PTH), calcitonin, calcium and magnesium levels in Group A (shaded columns and dotted lines) and Group B (blank columns and solid lines) pancreatitis parents. Plasma PTH concentrations (△) below the minimum detectable limit of the assay and exceeding 20 ng./ml. are excluded from the mean values shown.

in subjects with pancreatic diabetes.[24] Although the mean serum GH values in the first six hours following admission were lower in Group B patients, the wide variation in serum GH levels precluded an adequate interpretation of the differences observed. The failure to demonstrate differences in serum gastrin concentrations was not unexpected, as the gastrin response to an arginine infusion in chronic pancreatitis appears to remain intact.[25] Values for serum cortisol, cholesterol and triglyceride and NEFA concentrations were comparable in the two patient groups and did not distinguish patients with a previous history of pancreatitis.

Reasons for the unexpected elevation in plasma-immunoreactive parathyroid hormone concentrations in pancreatitis patients are uncertain. Our previous studies, however, have indicated that the raised PTH levels in AP are nonspecific in the sense that similar elevations are noted in stress states not associated with pancreatic disease.[1] As such the elevations in PTH observed may be related to the stress of the disease rather than specific metabolic alteration associated with the pancreatic inflammation itself. Although the hypocalcemia of AP has been attributed in part to inappropriate PTH responses,[26, 27] in those subjects with low PTH levels, total blood calcium values were not adversely compromised. Plasma calcitonin levels were comparable in the two patient groups but, just as with PTH, more extensive studies are required to accurately define the alterations of these hormones in acute and chronic pancreatitis.

Changes in hormone patterns in patients undergoing a second or subsequent attack of AP appear restricted to plasma glucagon concentrations and compared to metabolic responses observed in end-stage chronic pancreatitis, appear to be poor indicators of the natural course of the disease. The predictability, however, of the endocrine milieu in repeated acute pancreatitis episodes with regard to the metabolic abnormalities characterizing chronic pancreatitis, is probably a function of disease severity, number of previous episodes of AP and ultimately the degree of pancreatic parenchymal inflammation.

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Clinical Vignette

Achalasia of the Esophagus

Pneumatic Dilatation in a Four-year Old Boy

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A four-year old boy with achalasia of the esophagus was successfully treated with pneumatic dilatation, using the standard Browne-McHardy dilator, without incident. His subsequent course over 10 months has been uneventful.

Symptomatic achalasia of the esophagus is usually treated surgically in children under five years of age,[1-4] as mechanical dilatation by repeated passage of mercury-weighted or similar type dilators has produced only temporary relief.[2, 3] Pneumatic dilatation, frequently repeated, has been successfully performed in adults but has been considered too difficult or risky in young children.[1, 3, 5, 6] This paper presents a four-year old boy with achalasia of the esophagus successfully treated with pneumatic dilatation.

Case Report

A two-year old boy, with a history of vomiting solids and liquids immediately after meals since two months of age, was evaluated for failure to thrive. Appetite and activity were normal. Gestation and delivery were unremarkable except for recurrent vomiting during pregnancy and birth weight of 2.05 kg. An initial examination, weight was 7.65 kg. (< 3%); height, 80.62 cm. (< 3%) and head circumference, 42.5 cm. (25%). The only unusual physical finding was an undescended testicle on the left side. Laboratory data included normal complete blood count, urinalysis, total protein and albumin levels, serum electrolytes, quantitative immunoglobulins, urine metabolic screen, urine culture, stool examinations (culture, ova and parasites, occult blood, reducing substances), d-xylose tolerance test and human growth hormone level. Chest and skull x-rays were within normal limits. Radiological bone age was 15 months, chronological age was 25 months. Upper gastrointestinal series revealed dilatation of the esophagus with distal esophageal narrowing and disordered motility, consistent with achalasia.

The child was placed on a regular diet supplemented with Donnatal® before meals and at bedtime. Regurgitation persisted, with slow weight gain of 1.35 kg. in 12 months. Donnatal was replaced with a regimen of Bentyl®. At four years of age, his weight was 9 kg. (< 3%) and his height was 87.5 cm. (< 3%). Esophagram and ciné-esophagram revealed a tapered narrowing of the distal esophagus and proximal dilatation. A trickle of barium entered the stomach propagated by weak con-

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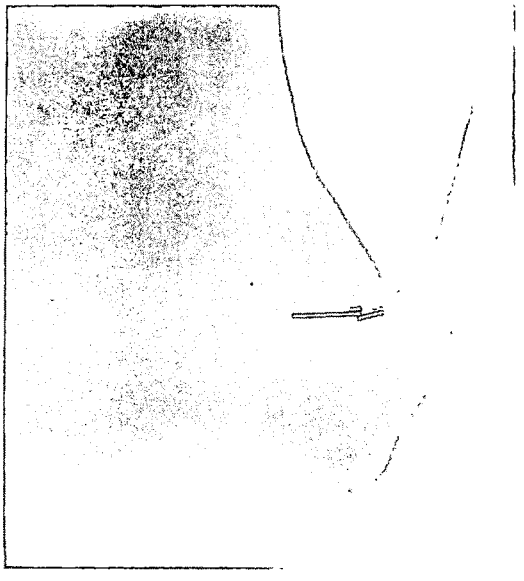


Fig. 1—A trickle of barium entered the stomach propagated by weak contraction waves (arrow).

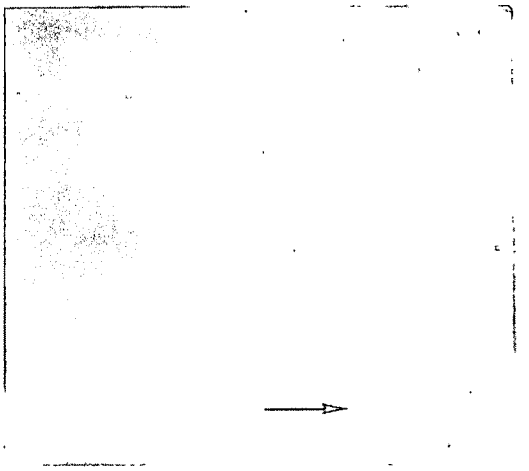


Fig. 2—Posttreatment esophagram showing good drainage of contrast material into the stomach. Minimal distal esophageal narrowing with slight dilatation (arrow).

traction waves (Fig. 1). Esophageal manometry could not be satisfactorily accomplished. Upper endoscopy under sedation with intravenous diazepam (Valium®) revealed a tapered narrowing of the distal esophagus and no peristaltic waves or esophagitis. Due to parental resistance to surgical treatment on religious grounds, pneumatic dilatation with the standard Browne-McHardy dilator was performed using a maximum of 150 mm. Hg. for three minutes. The posttreatment esophagram revealed good drainage of contrast material into the stomach, minimal distal esophageal narrowing with slight dilatation of the esophagus above that point (Fig. 2). He gained 1.25 kg. during the first two weeks after dilatation. A single episode of regurgitation has occurred in the ensuing 10 months.

Comment

Infantile achalasia is due to a decrease or absence of ganglion cells often associated with fibrosis and lymphocytic infiltration in the myenteric plexus (Auerbach's).[1-6]

Only 3-5% of infants and young children with achalasia develop symptoms.[1, 2, 5] Difficulty in swallowing solid food may be initially intermittent. Eventually, increasingly frequent and severe dysphagia, retrosternal pain and vomiting develop. Coughing, wheezing, recurrent pneumonia, anemia and weight loss are common and may contribute to failure to thrive.

The esophagus is tapered at the distal end and abnormal peristalsis and failure of relaxation of the gastroesophageal sphincter are seen in ciné-esophagrams.[1-5] Esophageal motility studies show elevated lower esophageal sphincter pressure, failure of relaxation of this zone with swallowing and lack of true peristaltic contractions in the body of the esophagus.[2, 5, 7] Esophagitis or retained food may be demonstrated by esophagoscopy.[2, 5, 8]

Dietary adjustments and anticholinergic medication have not been effective in these patients.[2, 8] Dilatation of the lower esophageal sphincter is frequently per-

formed in adults and children. Repeated passage of mercury-weighted or similar type dilators of increasing diameter provides temporary relief of symptoms. Swenson[9] employed mechanical dilatation up to three times before resorting to surgical treatment by cardiomyotomy (Heller procedure). To be effective, dilatation requires an actual tearing of the muscles of the lower esophageal sphincter, weakening but not destroying it. An expanding dilator is used and the pressure must be carefully controlled, since overstretching may cause rupture and associated mediastinitis. Other complications include gastroesophageal incompetence and aspiration. In the largest series in adults, Sanderson, et al,[10] observed good to excellent results in 65%.

Comparable data in children are not available. A single patient treated with pneumatic dilatation under five years of age has been reported.[11] The potential need for repeated dilatations and general anesthesia, and technical difficulties with passage, e.g. size and control of the dilator, have made its use unpopular in young children.[3, 10, 11]

The development of transthoracic esophagomyotomy has significantly diminished the need for pneumatic dilatation, still the initial mode of treatment in some centers. This operation has become the predominant treatment of choice in children and adults. Long-term follow-up results of surgery have been good to excellent in 80-94%, compared with 65-75% with pneumatic dilatation.[3, 4, 8, 10-13] This case report demonstrates that pneumatic dilatation can be successfully performed in young children, when surgery is not possible or allowed.

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Clinical Vignette

Gastrointestinal Tuberculosis Mimicking Cancer—A Reminder

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Tuberculous involvement of the gastrointestinal tract may be suspected in the presence of active pulmonary tuberculosis. This case demonstrates that tuberculous enteritis may develop in the absence of obvious pulmonary involvement. The diagnosis in such instances is established by a combination of roentgenographic studies and surgical exploration.

Introduction

Gastrointestinal tuberculosis is currently a rare entity because of pasteurization of milk and the general decline in pulmonary tuberculosis in the United States. Since this disease can mimic colonic carcinoma radiographically, physicians should be aware of this entity. The following report demonstrates that the disease may appear in patients without other evidence of tuberculosis.

Report of a Case

D. R., a 56-year old male was admitted to the Baltimore Veterans Administration Hospital complaining of intermittent inflammation of his hemorrhoids for the past five years. He had no abdominal pain, change in bowel habits or hematochezia. He consumed unpasteurized milk during his early childhood and traveled to Europe and Africa while serving in the military during World War II. He had also worked as a janitor on a tuberculosis ward in the 1950's and recalled an episode of pleuritis in 1953, from which he recovered without chemotherapy.

The patient was a well appearing black male who was afebrile. His chest was clear on auscultation. The abdomen was soft and nontender without palpable masses or hepatomegaly. Rectal examination revealed hemorrhoidal tissue that was minimally inflamed. His hematocrit was 43% and white blood count was 4,300/cu. mm. with a normal differential. Liver function studies and urinalysis were unremarkable. His chest x-ray revealed no evidence of old or active granulomatous disease. An intermediate strength PPD (5TU) produced a 12 mm. zone of induration in 48 hours. Sigmoidoscopy to 22 cm. was unremarkable but a barium enema demonstrated a filling defect several centimeters superior to the cecal pouch (Fig. 1). The area of constriction measured approximately 1½ cm. in length and remained after the administration of L-glucagon. At exploratory laparotomy, the wall of the ascending colon was thickened and the mesocolon, as well as the perigastric tissue, were surrounded by numerous

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Fig. 1—Classic apple-core lesion just distal to the cecum, due to mycobacterium tuberculosis.

enlarged nodes. Frozen section of one of these perigastric lymph nodes revealed an inflammatory reaction without definite evidence of neoplasm. Subsequently, a right hemicolectomy was performed.

The resected colon showed a constrictive lesion located approximately 2 cm. above the ileocecal valve. On section there was a 5 cm. transverse film ulcer with ragged edges. Microscopic examination of the lymph nodes and the colonic ulcer revealed prominent noncaseating granulomas (Fig. 2). Stains of this tissue for acid fast bacilli and fungi were negative. These findings were considered to be consistent with atypical granulomatous colitis with pericolic lymphadenitis as well as tuberculous enteritis. Three sputum samples did not contain tubercle bacilli on smear or culture. Culture of the perigastric lymph node, however, was subsequently positive for

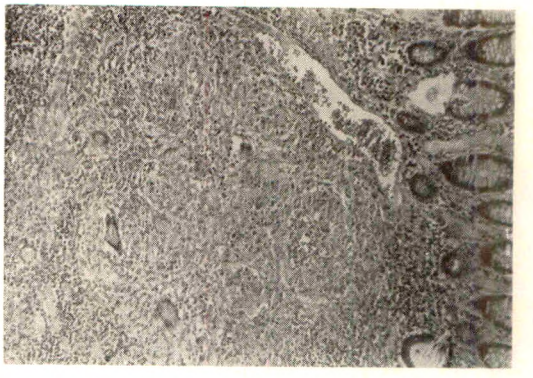


Fig. 2—Caseating granuloma in the bowel wall.

Myocobacterium tuberculosis. He was treated with isoniazid and ethambutol and has remained asymptomatic over a 16-month follow-up period.

Comment

Tuberculosis of the gastrointestinal tract is a rare disease in developed countries. After ingestion of unpasteurized milk, it may occur as a primary disease of the gastrointestinal tract. It can also be the result of dissemination from other foci of infection, primarily the lungs, either by hematogenous spread during the primary infection or by swallowing sputa from advanced cavitary lesions.[1] Prior to the use of effective chemotherapy, approximately 70% of the patients with advanced pulmonary tuberculosis had gastrointestinal involvement.[1, 2] This clinical entity becomes a diagnostic problem, however, when active pulmonary disease is absent.[3]

Although "napkin ring" lesions of the colon can be caused by a variety of diseases, including tuberculosis, amebiasis, actinomycosis, histoplasmosis, sarcoid and Crohn's disease, they are often considered to be cancerous unless the patient has signs or symptoms suggestive of these other illnesses. Clinical manifestations of tuberculous enteritis and carcinoma are nonspecific. Neoplasia is usually seen later in life and

symptoms are of shorter duration prior to the development of obstruction or severe anemia. Roentgenographically, barium contrast studies have been of great help in the diagnosis of colonic lesions. A persistent filling defect in the ileocecal region or ascending colon is the most frequent finding in tuberculous enteritis[4] but it is indistinguishable from a neoplastic lesion.

As these features do not usually differentiate between such disorders, abdominal exploration is usually necessary. The pathologic changes which are observed in intestinal tuberculosis are ulcerations which extend transversally around the bowel wall, leading to fibrosis and stricture.[5] This reparative thickening of the intestinal wall closely resembles a neoplastic change.[6] The mesenteric lymph nodes, which show caseating granulomas, are almost always involved, even when there is minimal bowel disease.[7] Other diseases of the bowel such as Crohn's disease, amebiasis, actinomycosis and histoplasmosis may present with a similar histologic picture.[8] Therefore, samples of the lesion and neighboring lymph nodes should be stained and cultured for fungi, protozoa, actinomyces and the tubercle bacillus. The importance of culturing the tissue obtained by biopsy or resection is emphasized in the case described. The growth of *Mycobacterium tuberculosis* from a mesenteric lymph node distinguished tuberculous enteritis from granulomatous colitis. Corticosteroids play an important role in the therapy of the latter disease[9] but may be harmful in tuberculosis in the absence of adequate antituberculosis therapy.

Obstruction of the bowel is the most common complication.[10] Fistulas occurring in approximately 25% of patients, may be external between the bowel and the skin or internal between the intestinal loops or between the bowel and the female pelvic organs.[11] Perforations of the bowel,[12] hemorrhage and intussusception have also been reported. The treatment of gastrointestinal tuberculosis is medical; chemotherapy with two antituberculous drugs, usually isonicotinic acid hydrazide and ethambutol hydrochloride, is adequate for both pulmonary and gastrointestinal tuberculosis.[13]

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Clinical Vignette

Gastric Bezoars—Spontaneous Resolution*

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Six cases of gastric phytobezoars were seen on fiberoptic gastroscopy over a period of four years during which time 1 400 gastroscopies were done. Four of these cases showed complete resolution of bezoars on repeat endoscopy during a follow-up period ranging from two weeks to one year. Our experience shows that, in the absence of gastric outlet obstruction, small bowel obstruction or other serious problems due to bezoars, they may not need surgical or aggressive medical treatment.

Introduction

Gastric bezoar is a large mass or concretion found in the stomach and occurs, usually, as a sequel of gastric surgery. Gastric bezoars may be formed of vegetable matter (phytobezoar) and may consist of undigested food, orange pith or persimmon (diospyrobezoar). They may consist of hair (trichobezoar) or other materials.[1-5] The word is probably derived from the Persian "pad zahr", meaning antipoison. Bezoars are also found in the stomach of goats and other animals and have been credited with therapeutic properties for maladies ranging from plague to impotence.[6] The incidence of postgastrectomy bezoars has been mentioned to be 9-14%,[7, 8] and postgastrectomy problems of abdominal pain, epigastric fullness and anemia have been ascribed to them. We report six cases of gastric bezoars seen on fiberoptic gastroscopy; four of them resolved spontaneously.

Methods and Results

Fourteen hundred fiberoptic esophagogastroduodenoscopic examinations for various upper gastrointestinal complaints were done at our institution over a four-year period. The details of the instrument used have already been described[9]. The case histories of six patients with gastric bezoars are summarized below.

Case Reports

Case 1:—A 59-year old white male with a five-year history of "peptic ulcer" disease was hospitalized because of upper abdominal pain. An upper gastrointestinal series showed a movable mass in the fundus of the stomach. The patient had no history of previous gastric surgery but had poor dentition. On gastroscopy a large greenish yellow mass (Fig. 1) was seen. Two weeks after admission he underwent operation for intractable peptic ulcer. No bezoar was found in the stomach; probably the bezoar was passed spontaneously in the interim.

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Fig. 1—Endoscopy showing a large yellowish-green mass in the body of the stomach.

Case 2:—A 65-year old white man with stage III Hodgkin's disease was admitted with epigastric pain and fullness. An upper gastrointestinal series showed a deformed duodenal bulb but the stomach was normal. The patient had ill-fitted dentures and had trouble chewing his food. Fiberoptic gastroscopy showed a greenish black bezoar in the body of the stomach; there was a small duodenal ulcer. He was treated with antacids. Two months later, repeat endoscopy showed no bezoar.

Case 3:—A 47-year old white man had undergone vagotomy and pyloroplasty seven years previously for duodenal ulcer. He was admitted with vague epigastric pain and fullness. Upper gastrointestinal series showed "increased gastric secretion". Fiberoptic gastroscopy showed an adherent greenish brown phytobezoar in the body of the stomach. The patient's symptoms improved without treatment. Repeat endoscopy ten months later showed no bezoar in the stomach.

Case 4:—A 54-year old white man with intractable duodenal ulcer underwent vagotomy and pyloroplasty six years before the present admission. In the meantime the patient developed scleroderma with reflux esophagitis. Fiberoptic gastroscopy showed a large green phytobezoar in the gastric fundus. An attempted fragmentation of the phytobezoar with endoscopic biopsy forceps was unsuccessful. Repeat endoscopy after one month showed a normal stomach.

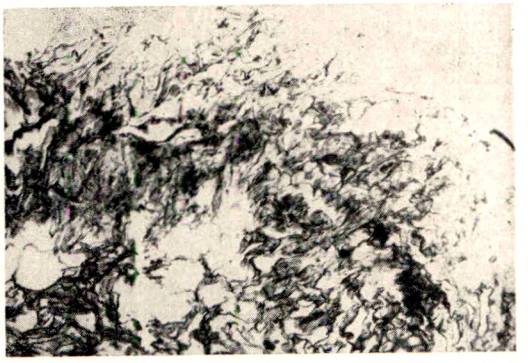


Fig. 2—Endoscopic biopsy showing vegetable fibers. (Hematoxylin and eosin, original magnification x100).

Case 5:—A 60-year old white man underwent hiatal hernia repair two years before the present admission. He complained of mild dysphagia. Upper gastrointestinal series showed some narrowing of the distal esophagus. On endoscopy, esophagitis and mild esophageal stricture were seen; in the stomach a large yellowish green phytobezoar was seen along the greater curvature. Biopsy of the phytobezoar performed by endoscope showed vegetable fibers (Fig. 2). The patient left the hospital two days later, refusing any treatment and was lost to follow-up.

Case 6:—A 44-year old white man who had vagotomy and pyloroplasty done two years before the present admission for intractable peptic ulcer disease was readmitted because of iron deficiency anemia and upper abdominal pain. He had mild epigastric tenderness. An upper gastrointestinal series showed a benign antral ulcer. Fiberoptic gastroscopy showed a



Fig. 3—Case 6, 5 × 2½ cm. gastric bezoar.

dark green mass along the greater curvature towards the posterior surface and a small benign antral ulcer. The mass, measuring 5 × 2½ cm., was dislodged by biopsy forceps introduced by endoscope and was removed (Fig. 3). The patient was treated with antacids and became asymptomatic.

It is to be noted that in two cases there was no prior gastric surgery and bezoars occurred when there was no reason for delayed gastric emptying. Three of the patients had undergone vagotomy and pyloroplasty and one patient had undergone hiatal hernia repair; it is probable that the latter patient might have had inadvertent vagotomy. Vagotomy alone seems to predispose to gastric bezoar formation; two cases of autovagotomy secondary to malignancy developed gastric bezoars.[10, 11] Three of our patients had poor dentition and ill-fitting dentures; inability to chew their food properly might have contributed to bezoar formation. A mild iron deficiency anemia was present in all of our cases. An upper gastrointestinal series showed the presence of bezoar in one case only; all were definitely diagnosed by fiberoptic gastroscopy.

Comment

The exact genesis of gastric bezoars is not completely understood. After gastric surgery, gastric atony and loss of gastric fragmentary capacity may be responsible. Other possible factors are reduction of pepsin and gastric acid, cementing effect of thick gastric mucin on ingested vegetable matter, inadequate chewing due to poor dentition and possible cementing effect of aluminum hydroxide. Delayed gastric emptying secondary to vagotomy or narrowing of the stoma may also be contributory factors[7, 12] Gastrointestinal phytobezoars have been reported, however, in patients who have not undergone gastric surgery and had good dentition.[12] In such cases, ingestion of persimmon or other fruit such as mango, or improperly cooked maize porridge which results in a gelatinous mixture,[13] may be responsible.

The common clinical features of gastric bezoars are upper abdominal pain, loss of weight, anorexia and anemia. They may cause intestinal obstruction.[13, 14] All of our paients had mild iron deficiency anemia and upper abdominal pain; none of them developed intestinal obstruction. The characteristic radiologic feature of gastric bezoars is a mobile mass coated with barium; however, sometimes they have been misdiagnosed as carcinoma.[13] In our series radiologic examination was helpful in one case; all were diagnosed by fiberoptic endoscopy.

Gastric bezoars have been successfully treated with various agents such as acetylcysteine, cellulase and papain with sodium bicarbonate. They have also been treated by lavage, liquid diet and emesis of the bezoar. Recently gastroscopic removal of gastric bezoars has been successfully carried out; it can be facilitated by the topical application of cellulase, and the use of a special basket introduced by endoscope.[15-25] Surgical treatment has been recommended in the past[5] and is necessary when gastric outlet obstruction or intestinal obstruction

results from the bezoar. One case of spontaneous resolution of phytobezoars has been mentioned.[26] Four of our cases showed spontaneous resolution; in the absence of obstruction, gastric bezoars may not need surgical or aggressive medical treatment.

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Clinical Vignette

Pseudotumor in the Mallory-Weiss Syndrome

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A Mallory-Weiss laceration with endoscopic and radiologic features of a submucosal tumor is described. Repeat examination showed complete resolution of the lesion.

Introduction

The Mallory-Weiss lesion is usually diagnosed only at endoscopy since in the vast majority of cases the laceration is too superficial to cause retention of contrast medium during upper gastrointestinal series. There are reports, however, in which the demonstration by barium study has been successful.[1, 2] This case was radiologically demonstrable since it presented features of a submucosal lesion.

Case Report

R. F., a 44-year old alcoholic male was admitted to Elmhurst General Hospital with hematemesis, melena, atrial fibrillation and tremulousness. During the preceding five days, he had been on an alcoholic binge and admitted to multiple episodes of self-induced emesis by manual pharyngeal stimulation to relieve abdominal pain and nausea. The onset of hematemesis brought him to seek medical care. On admission, the blood pressure was 130/90 mm. Hg. without orthostatic changes, the temperature was 38.3° C. There were no signs of chronic liver disease. The liver measured 14 cm. in vertical span. The hematocrit was 42%; the serum CO_2 content, 32 mEq./l.; the serum potassium, 2.8 mEq./l.; SGOT, 330 mU./ml.; SGPT, 91 I.U.; alkaline phosphatase, 139 I.U.; bilirubin, 3.2 mg.%.

Endoscopy on admission revealed a soft, bleeding longitudinally lacerated submucosal lesion at the lower end of the esophagus, overlying the Z line on the right

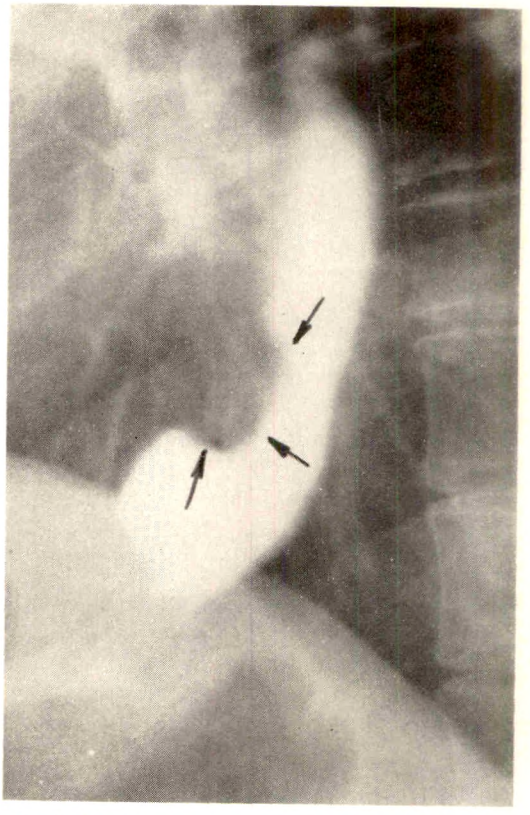


Fig. 1—Esophagogram showing rounded filling defect at the junction of the lower esophagus and a hiatus hernia.

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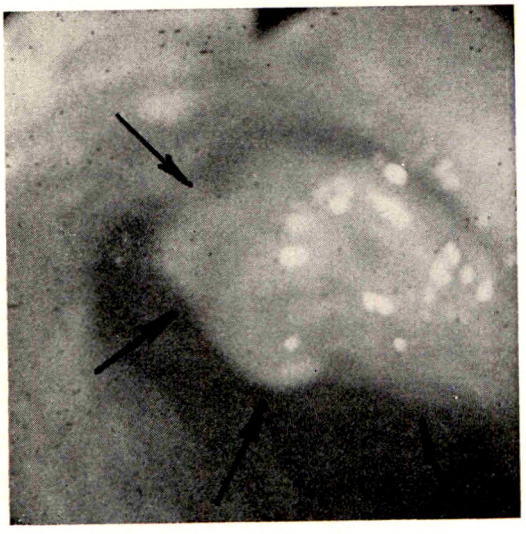


Fig. 2—Endoscopic view of the pseudotumor.

side. The lesion offered no resistance to the passage of the endoscope. There was a 3 cm. sliding hiatus hernia. The rest of the upper intestinal tract was normal. Barium study, 30 minutes afterward confirmed the endoscopic findings. The hematocrit progressively dropped from an admission level of 427% to 34% and remained stable at that level. Repeat endoscopy and upper gostrointestinal series five days after admission showed complete resolution of the lesion. Biopsy of the area revealed acutely inflamed granulation tissue in the mucosa.

The radiographic and endoscopic findings are illustrated in Figures 1 and 2.

Comment

This case presents the usual features of the Mallory-Weiss syndrome: alcoholism and a recent binge, protracted and forceful vomiting prior to the onset of hematemesis, a sliding hiatus hernia, a right-sided lesion, and a self-limited hospital course.[3, 4] The endoscopic and radiographic findings, however, were those of a submucosal tumor. Dagradi[4] described a soft, mound-like lesion in many of his patients but there was no radiographic documentation. Submucosal edema or blood possibly explains the findings. Complete disappearance of the pseudotumor five days after admission supports this interpretation.

Radiography is usually of little value in diagnosing this entity. Two previous case reports document a linear collection of barium at the site of the laceration.[1, 2]

As this case demonstrates, the appearance of a transient submucosal pseudotumor at the EG junction may also suggest the diagnosis.

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Clinical Vignette

Pancreatic Internal Fistula to the Left Pleural Cavity

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A case of recurrent pancreaticopleural effusion is presented. The pleural effusion with high enzyme and protein contents resulted from a pancreatic internal fistula to the left pleural cavity. A sinus tract passing through esophageal hiatus was demonstrated by the endoscopic retrograde pancreatography (ERP). Surgical intervention afforded complete relief of abdominal pain and elimination of the pleural effusion.

Introduction

Pleural effusion is frequently complicated with acute pancreatitis but most of such effusion is usually small and self-limited. Chronic pancreaticopleural effusion is commonly associated with either pancreatic pseudocyst or pancreatic internal fistula to the pleural cavity.[1, 2] A diagnostic clue is often provided with thoracentesis of the pleural fluid rich in protein and pancreatic enzymes. Preoperative demonstration of a fistulous tract is rarely successful. This paper presents a case of chronic pancreaticopleural effusion resulting from a pancreaticopleural fistula demonstrated by endoscopic retrograde pancreatography (ERP).

Case Report

A 47-year old male was admitted to Nagoya University Hospital on 13 March 1976 with a five year history of epigastric pain radiating to the back. He had been a heavy drinker over 20 years. Six months before admission, a left pleural effusion and an elevated serum amylase level were first noted at the other hospital. Medical treatments for pancreatitis and pleural effusion were not effective and a 7 kg. weight loss occurred in the past year.

Physical examination on admission revealed dullness to percusion and weak breath-sound in the lower half of the left chest and moderate tenderness in the epigastrium. There was no evidence of mass or free fluid in the abdomen.

Laboratory studies showed erythrocyte sedimentation rate of 45.5 mm./hr.; serum amylase of 340 Caraway units/100 ml. and total protein of 7.2 gm./100 ml. with normal fractions. Hemogram and liver function tests were within normal limits.

Chest x-ray examination revealed a pleural effusion in the left hemithorax (Fig. 1). There were no abnormal findings

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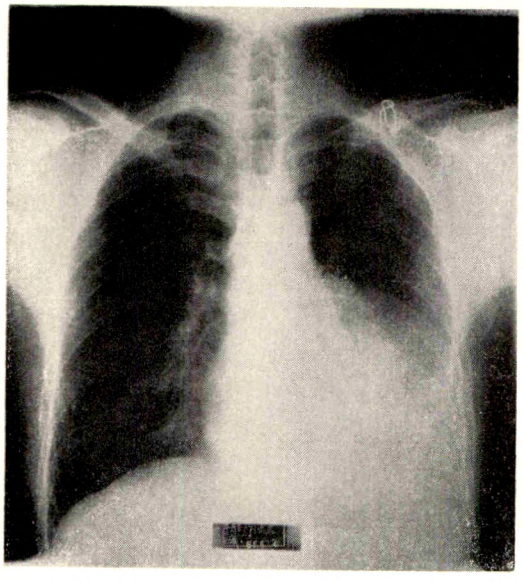


Fig. 1—Chest x-ray film, taken on admission, showing pleural effusion in the left chest.

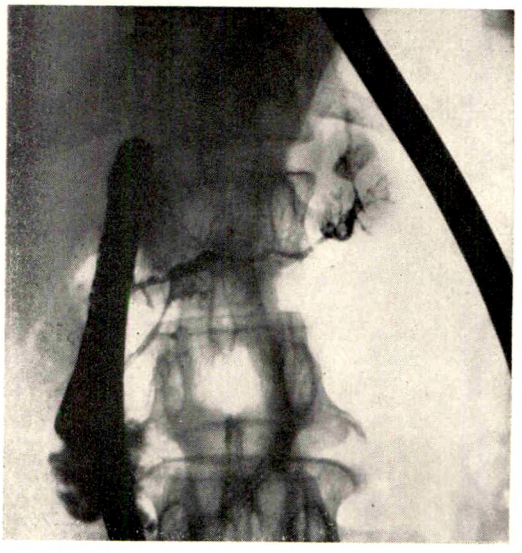


Fig. 2—Endoscopic retrograde pancreatogram showing dilated pancreatic ducts with irregularity and extravasation of contrast material which extends towards the esophageal hiatus by way of a sinus tract.

on x-ray of the upper gastrointestinal tract, biliary tract and colon.

The first thoracentesis produced sanguineous fluid with amylase concentration of 5,658 units/100 ml. One month later, the second thoracentesis yielded yellowish fluid with amylase concentration of 36,800 units/100 ml. and protein content of 5.6 gm./100 ml. No organisms were grown from the fluid and the results of cytology were negative.

The pancreozymin-secretin test[3] showed a decrease in volume and bicarbonate secretion with normal enzyme secretion. The pancreatic excretion test with 5,5-dimethyl-2,4-oxazolidinedione[4] revealed a great deficiency of the excretory function as observed in alcoholic pancreatolithiasis. An oral glucose tolerance test gave a diabetic curve. The response of immunoreactive insulin to the intravenous infusion of L-arginine was significantly reduced but that of immunoreactive pancreatic glucagon was within normal limits.

A selective angiographic study demonstrated an increase in vascularity and constriction of the splenic vein at the portion of the pancreatic body. An endoscopic retrograde pancreatography[3, 5] revealed irregularity of the main duct, marked dilatation of branches and extravasation of contrast material extending toward the esophageal hiatus (Fig. 2). These results of thoracentesis and ERP suggested direct communication between the pancreatic ductal system and the thorax, i.e. pancreaticopleural fistula.

Because of recurrent attacks of upper abdominal pain and persistent pleural effusion, an exploratory laparotomy was performed on 3 June 1976. On exploration, the liver and the gallbladder appeared normal but the pancreas was extremely hard and adhered firmly to adjacent structures and organs. A small pseudocyst was found in the body of the pancreas and communicated with the left thorax through the esophageal hiatus by way of a sinus tract.

Distal pancreatectomy was performed including removal of the cyst.

The patient's postoperative recovery was uneventful and the serum amylase level returned to normal.

Up to the present, he had experienced no recurrence of chronic relapsing pancreatitis or pleural effusion.

Histological studies of the resected specimen of the pancreas showed extensive fibrosis, loss of the parenchyma and marked dilatation of the ducts.

Comment

Pleural effusion, as a complication of acute pancreatitis, has an incidence varying from 3-17%.[6] This effusion either resolves as the intra-abdominal inflammation subsides or is easily eliminated by thoracentesis. On the other hand, chronic pleural effusion is characterized by massive effusion, high enzyme and protein contents and recurrence after thoracentesis.[2] The serum amylase level is usually elevated, probably due to absorption of amylase from the effusion. In our case, the effusion persisted over six months and the amylase and protein contents in the fluid were markedly elevated.

Various causes of amylase-rich pleural effusion have been presented. Chemical irritation of the diaphragmatic lymphatics is one of the causes of the effusion associated with pseudocyst of the pancreas.[7] The most probable cause of massive chronic effusion is a direct communication between the pancreatic ductal system and the pleural cavity. Sutton, et al[1] and Bergman, et al[8] reported a case of fistulization of the pancreatic pseudocyst to the left pleural cavity. Anderson, et al[2] reported five operative cases of chronic pancreaticopleural effusion. According to them, the fistulous tract passed through the aortic hiatus in two patients and the esophageal hiatus in three patients.

Smith, et al[9] emphasized usefulness of operative pancreatography for definite diagnosis of disruption of the main pancreatic duct and internal fistula. In our case, ERP demonstrated a sinus tract of pancreaticopleural fistulization.

Pancreaticopleural effusion is thought to be analogous to pancreatic ascites. In general, pancreatic internal fistula is treated effectively with surgical intervention. According to Cameron, et al,[10] the treatment of choice is caudal resection of the pancreas with excision of a sinus tract or cyst. Our patient received distal pancreatectomy with removal of the pseudocyst, which afforded complete relief of abdominal pain and elimination of pleural fluid.

Our present experience has shown that recurrent bouts of alcoholic pancreatitis may occasionally induce the formation of pancreatic pseudocyst followed by fistulization to the pleural cavity.

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Clinical Vignette

Effect of Acute and Chronic Administration of 5-FU on Pancreatic Secretion

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The administration of various dose schedules of 5-FU did not result in any alteration of pancreatic secretion. The findings would not support the thesis that the gastrointestinal side-effects of this potent cancer chemotherapeutic agent are the result of a toxic pancreatic insufficiency.

Introduction

5-fluorouracil (5-FU) is an antimetabolite which is widely used for the palliation of a variety of solid tumors, most notably carcinomas of the breast and the digestive tract. Its tumoricidal action is primarily due to the inhibition of the enzyme thymidylate synthetase which is necessary for the synthesis of DNA.[1] In addition, 5-FU is incorporated into the RNA of mammalian cells[2] and inhibits protein synthesis.[3]

The exocrine pancreas is an organ which actively synthesizes proteins vital for normal digestion. It is possible that 5-FU may have an effect on pancreatic function by virtue of its ability to inhibit its synthesis of proteins. Indeed, the frequent occurrence of gastrointestinal symptoms in patients receiving 5-FU may be in part related to pancreatic dysfunction.

It is the purpose of this study to determine the acute and chronic effects of 5-FU administration on pancreatic secretion in the dog.

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Methods

In order to determine the effects of 5-FU on the pancreas, six adult mongrel dogs were tested, using each as its own control. Pancreatic secretion was measured both before and after the administration of 5-FU at different dosage schedules.

Under general anesthesia Thomas fistulas were constructed in all dogs, facilitating cannulation of the pancreatic ducts and the collection of pancreatic juice.

After the dogs were fully recovered from surgery, secretin tests were performed to measure pancreatic function in the control period. 5-FU was then administered at various dosage schedules (Table I). Dog 1 received 12 mg./kg. daily for four days, then 6 mg./kg. every other day for 10 days. Dog 2 received 10 mg./kg. every other day for 14 days; after a 10-day rest period, the same dosage was resumed daily for seven days. Dog 3 was given 7 mg./kg. two times a week for seven weeks. Dogs 4, 5 and 6

TABLE I

DOSAGE SCHEDULES OF 5-FU

Dog no.	Quantity of 5-FU administered per dose (mg./kg.)	Frequency	Duration (days)
1	9	Daily	4
	6	Alternate days	10
2	10	Alternate days	7
	10 Day Rest Period		
	10	Daily	7
3	7	Bi-weekly	50
4, 5, 6	20	Daily	20

TABLE II

PANCREATIC SECRETION IN DOGS BEFORE AND AFTER THE ADMINISTRATION OF 5-FU

	Control period before 5-FU			Drug treatment period after 5-FU		
Dog no.	Volume cc./kg./30′	HCO_3 output mEq./kg./30′	Protein secretion mg./kg./30′	Volume* cc./kg./30′	HCO_3 output* mEq./kg./30′	Protein secretion* mg./kg./30′
1	1.69	4.47	14.10	2.31	4.31	41.14
2	2.82	4.02	75.05	3.03	3.87	77.64
3	3.83	4.82	118.49	3.25	5.03	107.87
4	1.96	3.45	31.54	1.92	3.40	31.02
5†	1.74	3.90	29.8	1.90	3.22	38.21
	2.61	5.92	47.7	2.79‡	5.02‡	57.59‡
6†	1.95	4.13	17.19	1.66	3.79	15.18
	2.30	4.78	32.22	1.70‡	3.79‡	34.05‡

* For dogs 1, 2 and 3 values represent means of each measurement during drug treatment periods.
† Results are first and second halves of double secretin test.
‡ Results obtained immediately after injection of 5-FU 20 mg./kg.

all received 5-FU at 20 mg./kg. daily for 20 days. In every case, the drug was administered as an intravenous bolus.

Secretin tests were performed on dogs 1, 2 and 3 at various times throughout the course of treatment with 5-FU (averaging

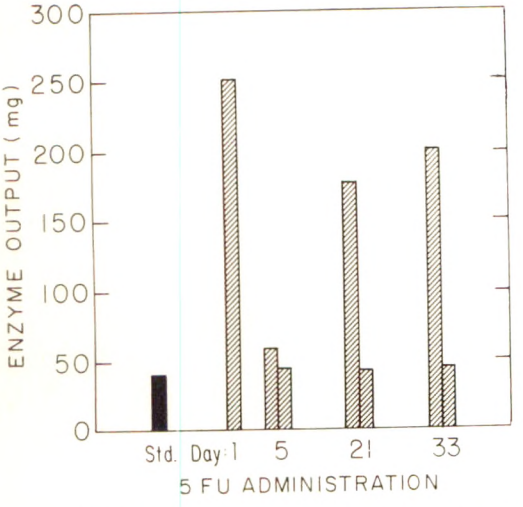


Fig. 1—Dog 1, sequential protein output responses to pancreatic stimulation before and after 5-FU administration.

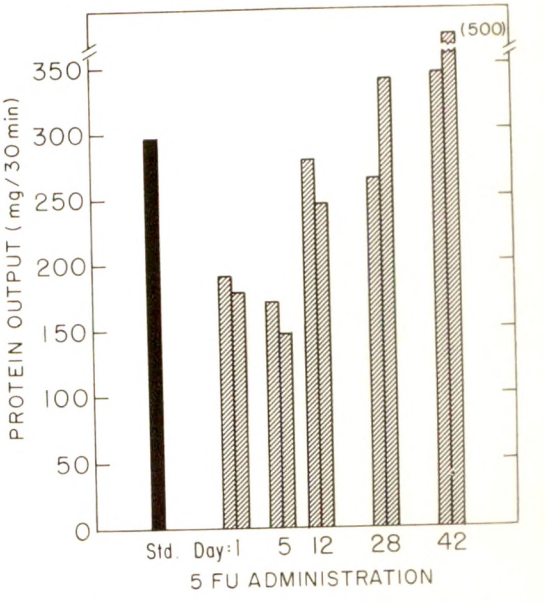


Fig. 2—Dog 3, sequential protein output responses to pancreatic stimulation before and after 5-FU administration.

every third day) as well as after the drug treatment period was completed. Repeat secretin tests in dogs 4, 5 and 6 were performed on the 21st day only, one day after the course of treatment with 5-FU was completed.

The secretin tests were performed as follows. Pancreatic juice was collected for a basal period of 15 minutes, after which time both secretin and cholecystokinin-pancreozymin (CCK-PZ) were given to stimulate pancreatic secretion. In dogs 1, 2 and 3 secretin and CCK-PZ were each given as an intravenous bolus at 4 U./kg. (augmented secretin test). In dogs 4, 5 and 6 secretin and CCK-PZ were administered as a continuous intravenous infusion at a dosage of 0.5 U./kg. over 30 minutes.

The stimulated pancreatic output was collected for 30 minutes at five-minute intervals. The volumes of pancreatic juice obtained during each collection period from each dog were measured. The fluids were analyzed for their contents of bicarbonate and protein.

In dogs 5 and 6 "double" secretin tests were done to measure any acute effects 5-FU might have on pancreatic secretion. Following the 30-minute collection period and a rest period of 30 minutes these two animals received an additional single intravenous bolus of 5-FU at 20 mg./kg. Secretin and CCK-PZ infusion were administered as before and collections from the stimulated pancreas proceeded for an additional 30 minutes.

Results

The results of the measurements of pancreatic secretion are summarized in Table II. Values for dogs 1, 2 and 3 in the drug treatment periods represent the means of the various measurements taken during this time interval. With two exceptions, described below, there were no significant differences between the volumes of pancreatic juice, its contents of bicarbonate, or in the rates of protein secretion before and after the administration of 5-FU.

In dog 1 there was an increase in the protein output by the pancreas during the drug treatment period. The values, however, showed a marked degree of fluctuation with each measurement (Fig. 1).

In dog 3 there was first a diminution followed by an elevation in the protein output as compared with values from the control period (Fig. 2).

The single "acute" bolus injection of 5-FU given to dogs 4 and 5 also had no effect on any facet of pancreatic secretion when compared with values obtained from the corresponding control periods.

Comment

The effects 5-FU will have on a given tissue are complex and depend upon multiple factors. The uptake of 5-FU depends on the tissue's vascularity and cellularity as well as on its metabolic rate.[4] 5-FU actually kills cells only when they are dividing[5] and one would expect greater effects on organs whose cells undergo a rapid turnover. Finally, although 5-FU is mainly catabolized in the liver, most normal cells have the ability to detoxify it and in many cases this may play a role in limiting its effects.

Although the pancreas is not an organ whose cells undergo rapid division, it is a metabolically active organ which synthesizes large quantities of protein. 5-FU was found to be effective in treating dogs with experimental pancreatitis, the conclusion being that the drug inhibited the production of proteins which would otherwise have caused autodigestion and necrosis.[3] 5-FU also protected pancreatic allografts in dogs from developing pancreatitis, presumably by the same mechanism.[6] In addition, the administration of 5-FU to rats caused structural changes in the pancreas which the authors interpreted as representing both the inhibition of protein synthesis and the blockage of discharge of already synthesized proteins from the cell.[7]

In the present study we found no consistent qualitative nor quantitative changes in the pancreatic secretion of the dog after the administration of 5-FU at a variety of dosage schedules. The changes in protein output noted in dog 1 were too erratic to be considered meaningful. The changes in dog 3, diminution followed by elevation of protein secretion, may reflect the response of the pancreas to injury. Much larger quantities of 5-FU, however, were given to dogs 4, 5 and 6 and any injurious responses should have been measurable here. These effects were not observed. Furthermore, there were no effects noted immediately following the "acute" injection of 5-FU.

It may be that 5-FU has effects only on the inflamed pancreas and not on the healthy organ. Alternatively, the proposed mechanism of improvement of pancreatitis by 5-FU through the inhibition of protein synthesis may be incorrect. There is no conclusive evidence that gastrointestinal side effects in patients receiving 5-FU are related to drug induced disturbances of pancreatic function.

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The Radiology Corner*

The Radiographic Diagnosis of Pica

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Pica, the ingestion of nonfood substances, is a significant public health problem in the United States which can often be detected by recognizing radiopaque material in the gastrointestinal tract on plain abdominal radiographs. In some cases, abdominal films may offer the first clue to the practice and be useful in determining the quantity of material eaten.[1-3] The ingestion of clay (geophagia) and starch is most often seen among poor Southern blacks, although it is also found in large Northeastern cities in residents who have migrated from the South. Other materials frequently ingested include dirt, coal, ice, chalk, pebbles, wood, plaster, hair, paper and cloth.

Pica may lead to abnormal nutrition and toxicity by any of four mechanisms. First, the ingested material may contain a large number of calories without providing other essential nutrients leading to obesity and iron deficiency anemia (starch ingestion).[4, 5] One of the authors (A. M.) is personally aware of a black laundress in New York City whose health was greatly jeopardized by her 202.5 kg. bulk. The patient steadfastly maintained that her food intake was actually very small and it was learned, only after hospitalization for weight reduction, that the real source of her obesity was the ingestion of several boxes of laundry starch every day.

Second, the material may be consumed in large quantities and displace the consumption of more nutritious substances resulting in malnutrition (*cachexia africanus* secondary to geophagia).[6] The latter syndrome was reported with great frequency during slave times in the United States and was considered an economic problem by slave owners and traders. The patients developed lethargy, smooth, shiny edematous skin and finally heart failure. It was believed by some to represent a form of suicide and by others a reflection of limited food availability.

Third, the ingested material may contain toxic substances (lead poisoning secondary to the ingestion of old paint chips)[7] or large quantities of normal nutrients causing problems in a compromised patient (hyperkalemia in renal failure patients with geophagia).[8] Finally, the material may serve as a mineral exchanger resulting in iron deficiency anemia and hypokalemia (geophagia).[9, 10]

The majority of patients with geophagia present with symptoms secondary to iron deficiency anemia. Some authorities believe that mineral deficiencies such as zinc, iron or calcium create abnormal cravings for clay or starch. Most patients, how-

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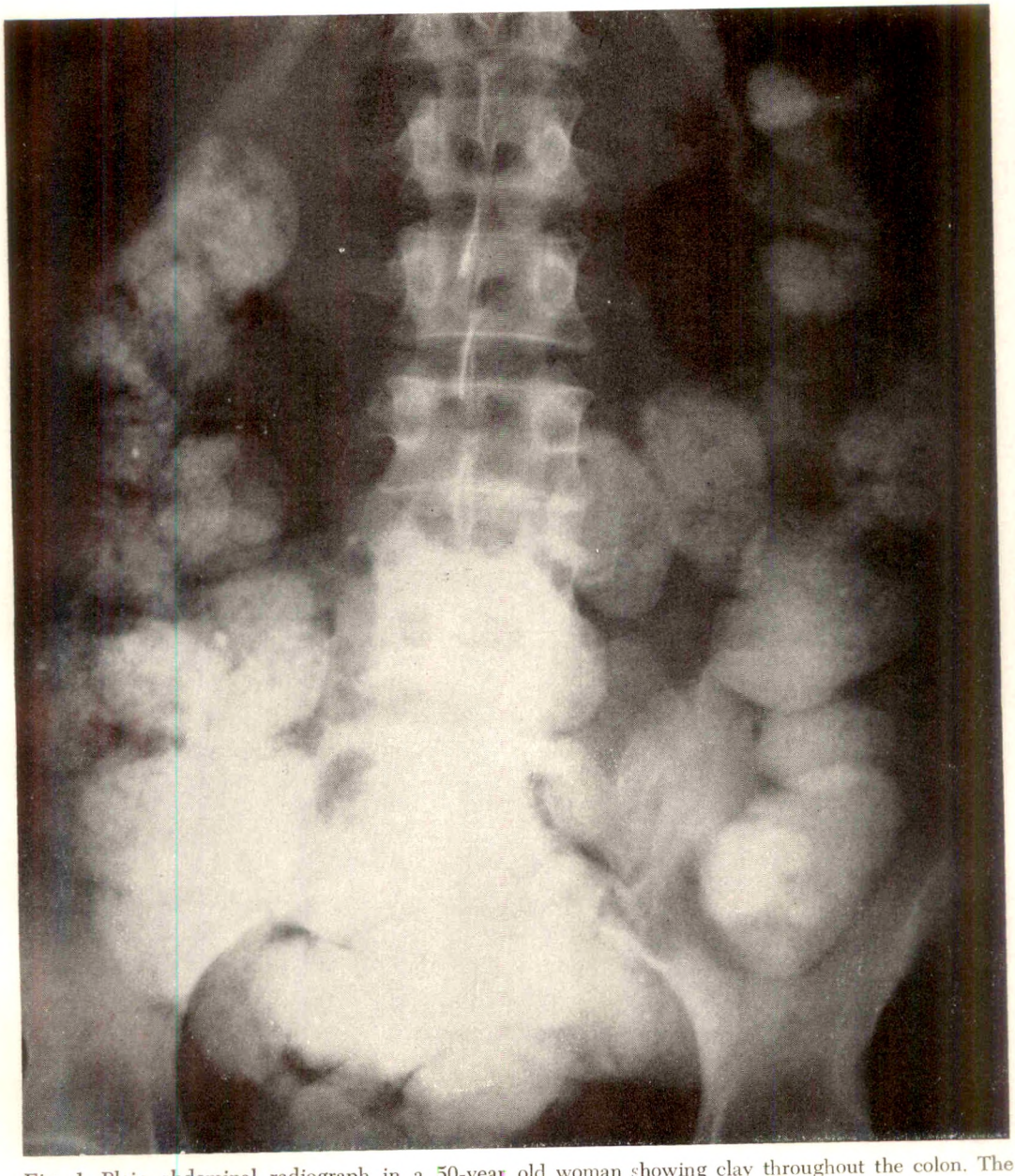


Fig. 1—Plain abdominal radiograph in a 50-year old woman showing clay throughout the colon. The patient had severe hypochromic microcytic anemia.

ever, begin eating these materials after being introduced to the practice by a friend or relative. It is likely that the ingested material induces a secondary iron deficiency anemia either by binding the iron to the clay particles or by acting as an ion exchange resin, or that its ingestion provides bulk in the diet low in essential nutrients which displaces more nutritious foods.[9-13]

Children, particularly those in the 18-35 month age group, are in an active stage of oral development and often ingest

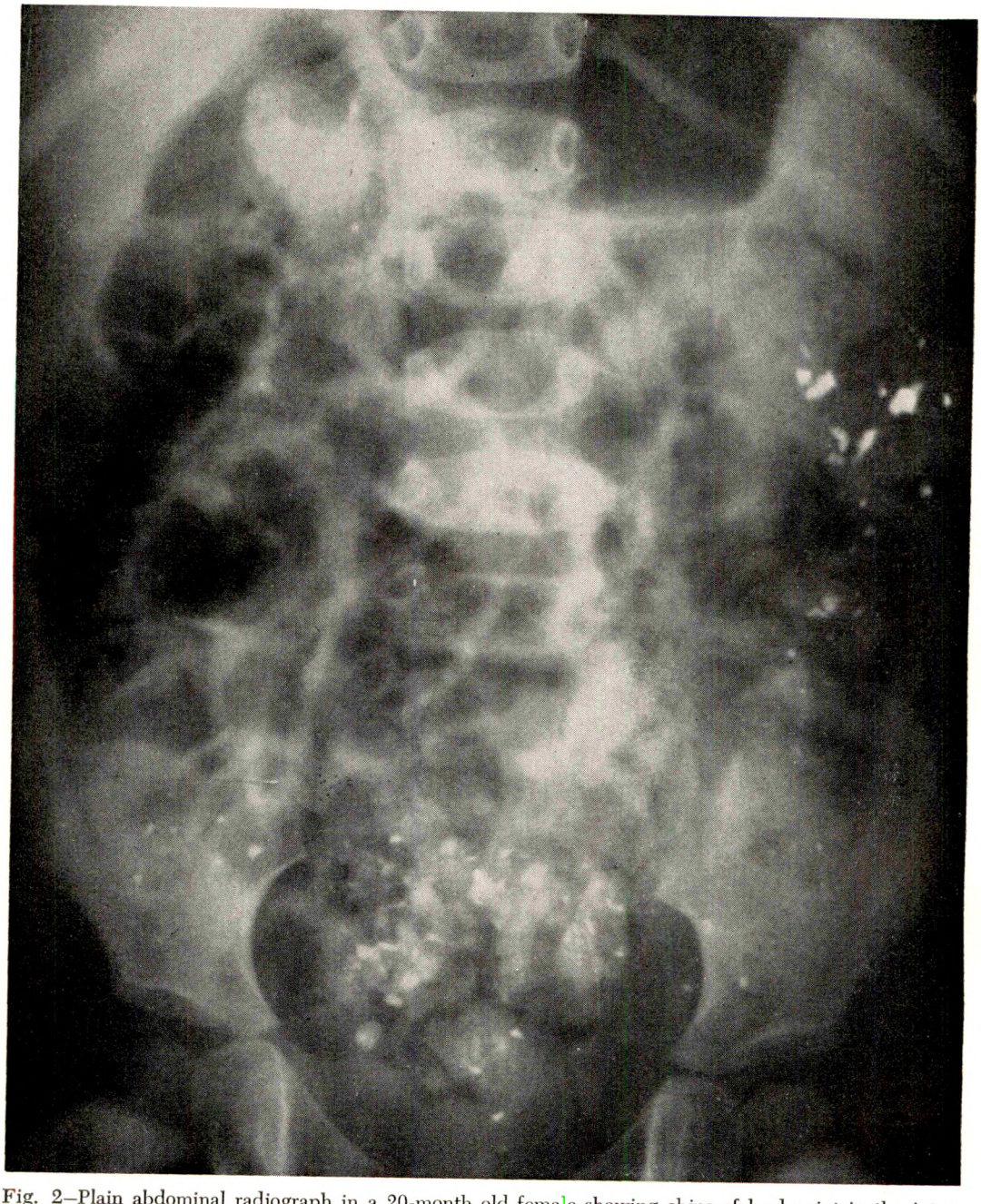


Fig. 2—Plain abdominal radiograph in a 20-month old female showing chips of lead paint in the intestine. The patient had clinical and radiological evidence (lead lines) of lead poisoning (Courtesy of Guido Currarino, M.D.).

a wide variety of foreign materials. In slum areas where lead based paint still covers the walls, ingestion of paint chips leads to lead poisoning. These children may present with symptoms of anemia, vague abdominal pain or failure to thrive. Acute lead intoxication results in lead encephalopathy, severe seizures, coma or death.[7, 14]

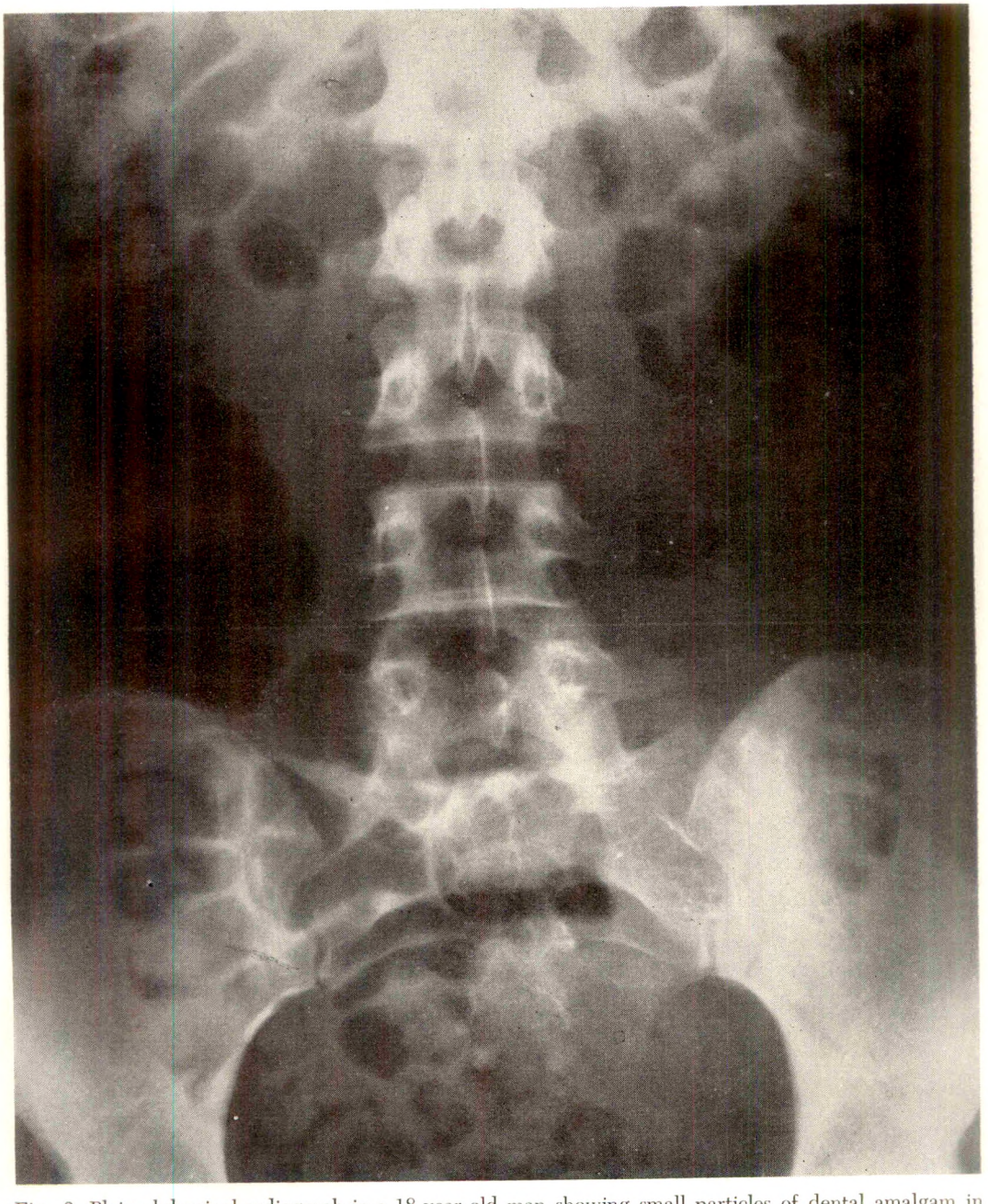


Fig. 3—Plain abdominal radiograph in a 18-year old man showing small particles of dental amalgam in the colon following treatment for dental caries.

Other reported complications of pica include a zinc deficiency syndrome,[15] intestinal obstruction, bezoar formation and a syndrome of hypogonadism, hepatosplenomegaly and geophagia.[16]

The practice of clay and starch eating was studied extensively in a group of pregnant black women in a prenatal clinic.[17] The results showed that anemia was prevalent but the infants born to these mothers

suffered no untoward effects when compared to a control group.

The plain abdominal radiograph can play an important role in the diagnosis of pica due to clay or paint (Figs. 1 and 2).[1, 3, 6] Both materials are identifiable on the radiograph because of their high mineral content. Other substances such as starch, newspaper and cigarettes are not readily apparent. When anemia is profound, there may be radiographic evidence of splenomegaly, cardiomegaly and congestive heart failure as well as the presence of radiopaque material in the intestine. Radiopaque material in the intestine due to radiographic contrast materials, opaque medications[18] and ingested dental amalgam following treatment of dental caries must be excluded (Fig. 3). The detection of pica on the abdominal radiograph is particularly significant in patients in whom the condition is not suspected clinically. This is likely to occur in areas where pica is rare and consequently, the physician is not cognizant of the problem.

Identification of the ingested agent on plain abdominal films is dependent upon the volume of material present as well as its radiopacity.[13] The latter is determined by the concentration of high atomic number minerals in the material such as silicon and calcium in clay.

Black radiographic technologists in the Department of Radiology at the Parkland Memorial Hospital were surveyed, and seven out of nine stated they had at some time eaten clay. All ingested it on a sporadic basis and consumption increased when they returned home to various rural towns in Texas. All stated that "folks" from their hometowns ate clay extensively, some baked it into various dishes such as brownies. The clay was frequently baked prior to eating because it was preferred dry and crumbly. East Texans eat a white clay and West Texans, a red clay. Each have a strong preference for their own variety. The two technologists who personally had never eaten clay had family members and friends who did eat it. Both of these technologists were from Dallas rather than rural areas. In addition, one technologist's mother ate large amount of African violet potting soil which she purchased in sterile bags from a garden store. None of these people appeared to be abnormal regarding their nutritional status.

The technologists were asked to survey their family members as to why they ate this material. The consensus was that they had been introduced to the habit by friends or relatives and had subsequently acquired a taste for the material. Most would only eat a certain clay from their area, carefully washed and baked. The white clay is described as being creamy and slightly sweet. The red clay is reported to be gritty and slightly tart.

Pica is endemic in India where clay and dirt are eaten but the preferred material is charcoal (Vena Dulate, M.D.—personal communication). This habit is not only seen among the poorer groups but is indulged in by the middle and upper classes as well. The major complications are iron deficiency anemia and, to a much lesser degree, intestinal obstruction.

The nutritional disturbances which result from pica are related to the volume of material consumed as well as to the content of toxic contaminants. It is almost certain that ingestion of small amounts is a harmless habit. When, however, large volumes are consumed, significant abnormalities may occur. In either case, the presence of pica can often be established by detecting radiopaque material in the gastrointestinal tract on plain radiographs of the abdomen.

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The Last Page

Questions in Gastroenterology

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The Last Page appears as a regular feature in each issue of The American Journal of Gastroenterology.

The questions that follow have been prepared exclusively from material in the current issue of the Journal and the page on which the answer can be found is indicated with each question.

One way for regular readers of the Journal to utilize this feature is to scan *The Last Page* and attempt to answer the questions before reading the Journal. Then, when the articles have been read, return to *The Last Page,* again try to answer the questions and finally refer to the page locations that are provided in order to confirm your answers.

For each question, one or more responses may be correct, or none may be correct.

1. IN ESOPHAGEAL MANOMETRY:

   A. A rapid infusion rate is needed to compensate for high catheter compliance.

   B. Catheter resistance to flow will elevate base line pressure.

   C. A low infusion rate allows the use of a catheter of small internal diameter.

   D. The esophageal body is generally 20-22 cm. in length.

(Page 23)

2. RISK FACTORS FOR CARCINOMA OF THE STOMACH INCLUDE:

   A. Blood group B.

   B. Previous distal partial gastrectomy.

   C. Low levels of serum gastrin.

   D. A high dietary intake of vegetables containing ascorbic acid.

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3. IN TESTING CONTROLS VERSUS PATIENTS WITH ACTIVE PEPTIC ULCER DISEASE IT WAS OBSERVED THAT:

   A. Both the basal (BAO) and pentagastrin-stimulated (PAO) acid and pepsin (PPO) outputs in the nonulcer group were significantly lower than in the acute ulcer group.

   B. There was appreciable overlap in the two groups in BAO, PAO and PPO.

   C. There was no overlap in the basal pepsin output.

   D. No patient had a basal pepsin output of more than 100,000 pU./hr. unless an ulcer was present.

(Pages 46 and 47)

4. PROSTAGLANDIN E_1:

   A. Inhibits gastric acid secretion.

   B. Inhibits gastrin released by acetylcholine irrigation of the antrum.

   C. Increases gastric mucosal blood flow.

   D. Stimulates cyclic AMP formation and adenyl cyclase activity in many systems.

(Page 52)

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5. CONCERNING COMPLICATIONS OF VAGOTOMY:

A. There is an excellent correlation between the response to insulin stimulation for acid and recurrent ulceration after surgery.

B. Some studies found no difference in the incidence of diarrhea between truncal and selective vagotomy.

C. Bethanecol may be useful both in gastric retention and in postvagotomy diarrhea.

D. Incapacitating diarrhea is treated by the interposition of a 25 cm. reverse jejunal segment at the ligament of Treitz.

(Page 57)

6. LIVER SCANNING:

A. Is a safe procedure that should be used routinely in the evaluation of patients with hepatobiliary disease.

B. Can be misleading and harmful almost as often as it is helpful.

C. Has a high diagnostic accuracy in identifying cancer in liver without other disease.

D. Is useful when objective evidence is required for the evaluation of cancer chemotherapy.

(Page 64)

7. IN A GROUP OF PATIENTS WITH ACUTE PANCREATITIS, THOSE WHO HAVE HAD PREVIOUS PANCREATIC INFLAMMATION TEND TO HAVE:

A. High blood sugar values.

B. Lower levels of PTH.

C. Lower serum insulin levels in relation to the prevailing hyperglycemia.

D. A significantly lower increase in glucagon concentrations.

(Page 70)

8. ACHALASIA OF THE ESOPHAGUS IN CHILDREN:

A. Is usually treated surgically in children under five years of age.

B. Responds to dietary adjustments and anticholinergic medication.

C. Is usually treated with pneumatic dilatation.

D. Responds transiently to passage of mercury-weighted dilators of increasing diameter.

(Pages 74 and 75)

9. GASTROINTESTINAL TUBERCULOSIS:

A. Can mimic colonic carcinoma radiographically.

B. May appear in patients without other evidence of tuberculosis.

C. Occurred in 10% of patients with advanced pulmonary tuberculosis prior to the use of effective chemotherapy.

D. May be complicated by obstruction of the bowel and fistula formation.

(Page 78)

10. BEZOARS:

A. Consisting of hair are called trichobezoars.

B. Consisting of undigested food, orange pith or persimmon are called phytobezoars.

C. When formed of vegetable matter are called diosypyrobezoars.

D. Derive from the Persian "pad zahr" meaning antipoison.

(Page 79)

11. THE USUAL FEATURES OF THE MALLORY-WEISS SYNDROME INCLUDE:

A. Protracted and forceful vomiting prior to the onset of hematemesis.

B. A sliding hiatus hernia.

C. A self-limited hospital course.

D. A left-sided lesion.

(Page 84)

12. PLEURAL EFFUSION ASSOCIATED WITH PANCREATITIS:

A. Has an incidence varying from 3-17% in acute pancreatitis.

B. Can be due to chemical irritation of the diaphragmatic lymphatics by a pseudocyst.

C. If chronic, usually results from a direct communication between the pancreatic ductal system and the pleural cavity.

D. Is best treated by caudal resection of the pancreas with excision of the sinus tract or cyst.

(Page 87)

13. 5-FLUOROURACIL:

A. Inhibits the enzyme thymidylate synthetase which is necessary for the synthesis of DNA.

B. Is incorporated into the RNA of mammalian cells and inhibits protein synthesis.

C. Is effective in treating dogs with experimental pancreatitis.

D. Causes alterations in pancreatic secretion that could explain its gastrointestinal side-effects.

(Page 92)

14. PICA MAY LEAD TO ABNORMAL NUTRITION AND TOXICITY BY:

A. Providing a large number of calories without providing other essential nutrients.

B. Displacing the consumption of more nutritious substances.

C. Containing toxic substances.

D. Serving as a mineral exchanger.

(Page 94)

Answers to Questions in *The Last Page*

The following are the answers to the questions which appeared in *The Last Page* during the six months, commencing with the January, 1978 issue. Comments from our readers concerning this feature are welcomed. The next set of answers for the period from July to December, 1978, will appear in the January, 1979 issue.

January, 1978

1. All
2. All
3. All
4. All
5. A,D
6. C,D
7. B,C,D
8. A,B,C
9. A,C,D
10. All
11. C,D
12. All
13. A,B
14. B,C,D
15. B,C,D
16. All

February, 1978

1. A,B,D
2. A,B,C,
3. A,B,D
4. A,C
5. B,C,D
6. All
7. All
8. B,D
9. B,C,D
10. All
11. A,B,C
12. A,C
13. B,C,D

March, 1978

1. A,C
2. A,B,C
3. B,C,D
4. All
5. All
6. C,D
7. C
8. All
9. A,B
10. All
11. A,B,C
12. C
13. None
14. A,C
15. B,C,D
16. B,C,D,
17. All
18. A,C,D
19. D
20. B,C
21. A,B
22. A,D
23. A,B,D
24. All
25. A,C,D
26. All
27. A,C,D

April, 1978

1. A,B,C
2. B,C,D
3. A,B,D
4. A,C,D
5. A,B,C
6. B,C,D
7. C,D
8. All
9. B,C
10. A
11. B,C,D
12. B,C
13. A,D
14. A,B
15. A,D

May, 1978

1. B,C
2. A,C,D
3. A,B,C
4. All
5. A,B,D
6. B,D
7. A,B
8. B,C
9. A,C,D
10. All
11. B
12. A,C,D
13. All
14. C
15. All
16. All
17. C

June, 1978

1. All
2. All
3. B,C
4. B,C
5. A,C,D
6. A,C
7. A,C
8. A,B,C
9. A,B
10. A,B,D
11. A,D
12. B,D
13. D

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Vol. 70, No. 1
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SELECTED ABSTRACTS FOR GASTROENTEROLOGISTS

Influence of isoproterenol and cholestyramine on acute gastric mucosal ulcerogenesis. Ritchie WP, Jr., Shearburn EW: Gastroenterology 73:62-65, 1977.

The pathogenesis of stress ulcers is still an enigma and the treatment of bleeding stress ulcers distressingly unsuccessful.

The currently dominant hypothesis on the genesis of stress ulcers implicates the combined presence of three factors: 1. intraluminal acid, 2. increased back diffusion of H^+ across an injured mucosa and 3. gastric mucosal ischemia.

In this elegant experimental study, the protective effect of isoproterenol and of cholestyramine in experimentally induced stress ulcers in dogs was demonstrated.

Intra-arterial isoproterenol afforded protection even though hydrogen ion back diffusion was not altered; cholestyramine proved effective by preventing back diffusion of hydrogen ions.

DEMETRIUS PERTSEMLIDIS, M.D., F.A.C.G.

Interaction of synthetic 10-Tyrosyl analogues of secretin with hormone receptors in pancreatic acinar cells. Gardner JD, Conlon TP, Beyerman HC, et al: Gastroenterology 73:52-56, 1977.

The field of intestinal polypeptide hormones and their receptor sites in their target organs is advancing with explosive rapidity. In this paper, two distinctly different receptors for secretin and vasoactive intestinal polypeptide (VIP) present in pancreatic acinar cells were tested. These two classes of hormone receptors were able to distinguish four synthetic analogues of secretin with only minor differences in molecular structure.

Thus, the high affinity or specificity of hormone receptors for secretin in the acinar cells of the pancreas and the importance of the amino-terminal group in the secretin modecule have been confirmed.

DEMETRIUS PERTSEMLIDIS, M.D., F.A.C.G.

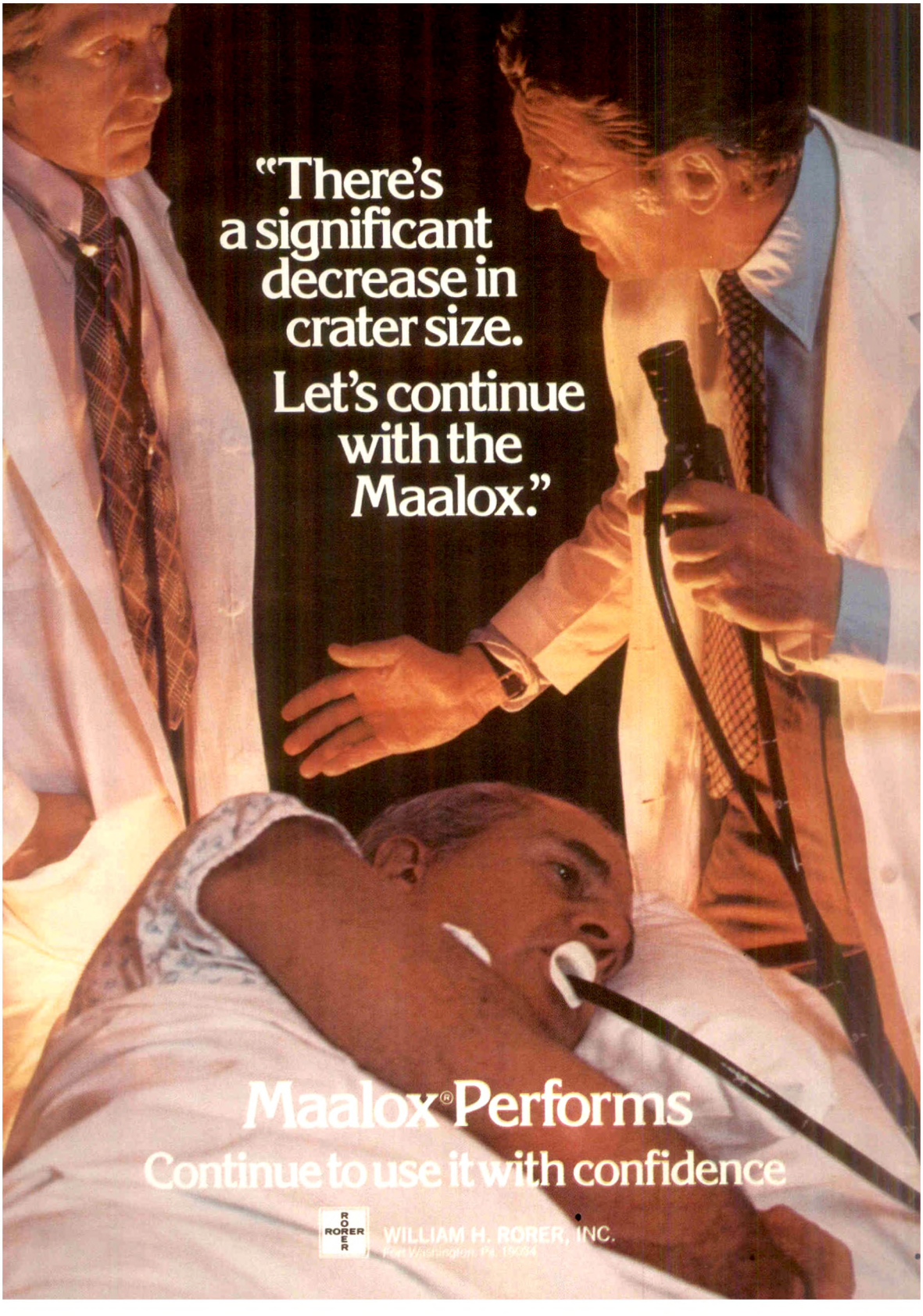
Percutaneous cholangiography with the Okuda needle. Hinde GDB, Smith PM, Craven JL: Gut 18:610-614, 1977.

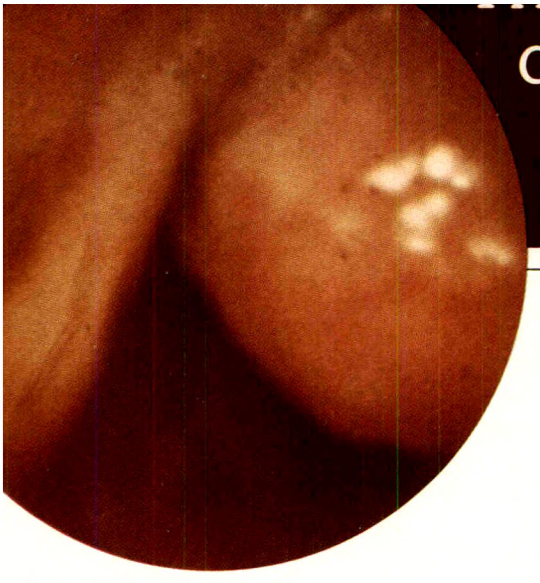
Percutaneous transhepatic cholangiography is becoming increasingly useful. With refinement in needle size by Okuda, the incidence of biliary leaks has been reduced and the diagnostic accuracy increased through the ability to enter a nondilated biliary duct system.

This technic, less cumbersome than ERCP and laparoscopy, is promising to become a routine study in cases where mechanical obstructive cholestasis cannot be differentiated from intrahepatic cholestasis.

In this paper, the authors describe successful demonstration of the bile duct anatomy in 41 of 42 cases with subsequent confirmation by laparotomy, necropsy or liver biopsy.

DEMETRIUS PERTSEMLIDIS, M.D., F.A.C.G.


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dysphagia of 1½ years' duration.

Physical exam is unrevealing. X-ray studies are inconclusive.

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A 56-year-old man was seen because of increasingly severe dysphagia of one and a half years' duration. At the time of admission, the patient could take only liquids. Physical examination was unrevealing.

A filling defect of the midesophagus was observed by the radiologist. On several projections it appeared to be extrinsic, although an intrinsic lesion, such as leiomyoma, could not be excluded.

Esophagoscopy was performed, and a round submucosal tumor thought to be a *leiomyoma* was identified at the level of 28 cm from the incisor teeth. The patient refused surgical intervention.

Causes of dysphagia may include esophageal carcinoma, achalasia, lower esophageal ring or esophageal web, as well as benign neoplasm. Benign tumors are rare and when detected are usually only incidental findings. Such tumors may, however, become symptomatic upon reaching a large enough size. Such tumors are most often *leiomyomas*, which can partially obstruct the esophageal lumen. Characteristically, they develop central ulceration and hemorrhage.

Case discussion based on *The Clinical Significance of Esophagoscopy* by Bernard M. Schuman, M.D., one in a series of monographs made available by Roche Laboratories in fulfillment of its commitment to continuing education in gastroenterology. This case history illustrates the diagnostic use of endoscopy; it does not represent an indication for Librax therapy.

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Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows: "Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Physical and psychological dependence rarely reported on recommended doses, but use caution in administering Librium® (chlordiazepoxide HCl) to known addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions) reported following discontinuation of the drug.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.**

As with all anticholinergics, inhibition of lactation may occur.

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established.

Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.

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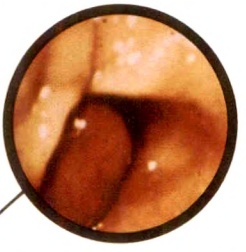
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THE American Journal OF Gastroenterology

A Journal of Clinical Gastroenterology

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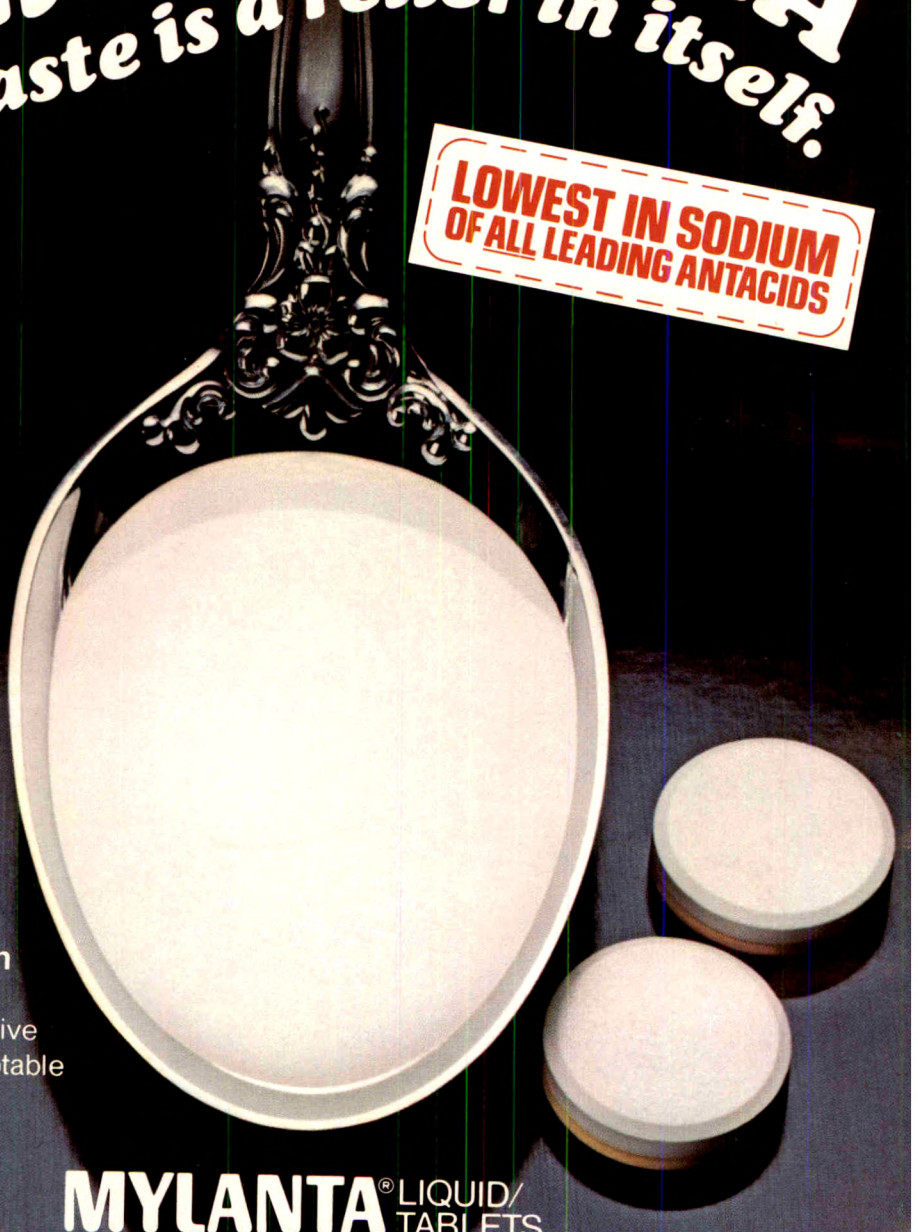
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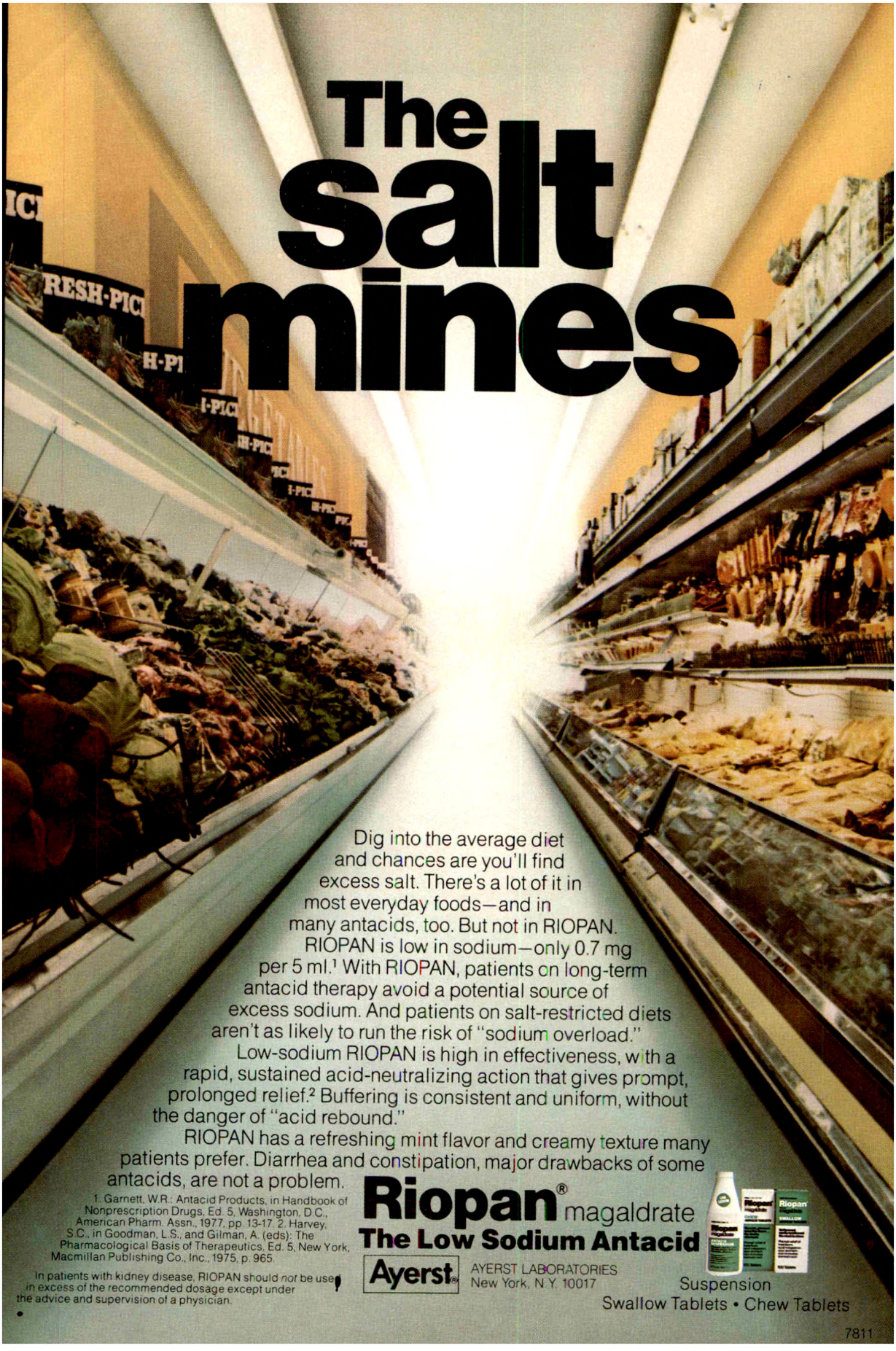


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1. Garnett, W.R.: Antacid Products, in Handbook of Nonprescription Drugs, Ed. 5, Washington, D.C., American Pharm. Assn., 1977, pp. 13-17. 2. Harvey, S.C., in Goodman, L.S., and Gilman, A. (eds): The Pharmacological Basis of Therapeutics, Ed. 5, New York, Macmillan Publishing Co., Inc., 1975, p. 965.

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References to an article with *3 or less authors:*

1. Robinson AS, Sommer DA, Levinson M: Transfiberscopic removal of esophageal polyps. Am J Gastroenterol 61:297-300, 1974.

References to an article with *more than 3 authors:*

2. Starzl TE, Lee IY, Porter KA, et al: The influence of portal blood upon lipid metabolism in normal and diabetic dogs and baboons. Surg Gynecol Obstet 140:381-388, 1975.

Reference to a book:

3. Reuter SR, Redman HC: Gastrointestinal Angiography. Second Edition. Philadelphia, W. B. Saunders Company, 1977.

Reference to an article in a book:

4. Ansel HJ: Normal Pancreatic Duct. *In:* Atlas of Endoscopic Retrograde Cholangiopancreatography. Edited by Stewart, ET, Vennes JA, Geenen JE. St. Louis, The C. V. Mosby Company, 1977, pp. 43-47.

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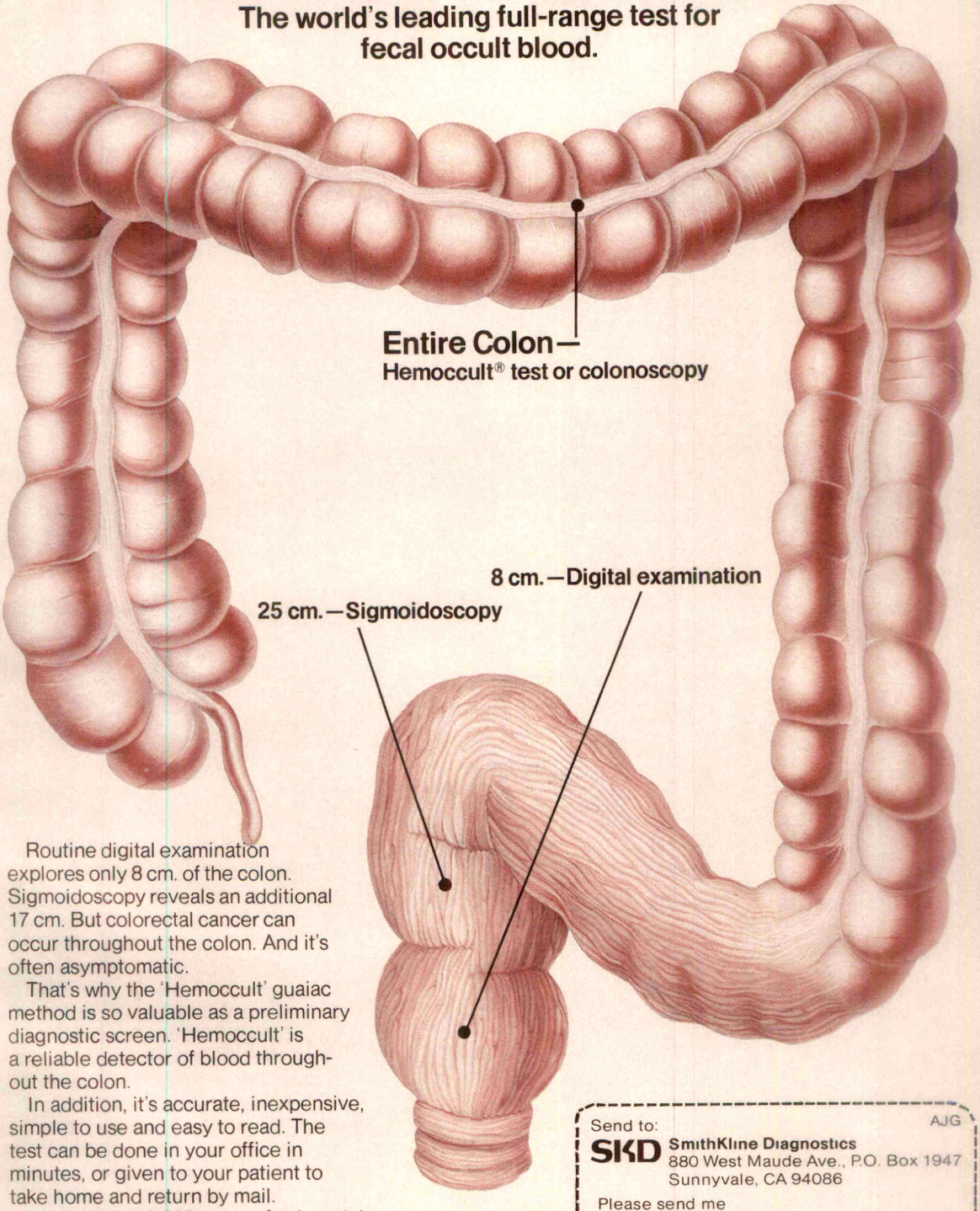
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Avoid U.C. flare-up over the long haul

4½ times greater relapse rate for non-Azulfidine-treated patients revealed in a double-blind study.[1]

Your patients need your guidance to help prevent recurrence of ulcerative colitis. They may not be aware that U.C. with all its pain and discomfort is a chronic disease. Several investigators[2-6] have shown that the best way to control relapse is to medicate over the long-term with Azulfidine (sulfasalazine, N.F.). Further proof is contained in the double-blind "Truelove" study.[1]*

Ulcerative colitis patients were symptom-free at the start of this controlled study. All had been maintained on Azulfidine for from one to over five years. During the six-month trial, more than 54% of the placebo group suffered relapse—a rate 4½ times greater than the 12.1% who showed a recurrence of symptoms in the Azulfidine-treated group! The therapeutic action of Azulfidine was credited with the striking difference in these figures.

The only side effects among the study group were two cases of nausea and one of headache. (These symptoms ceased without a change in dosage when patients returned to open therapy.)

The authors concluded that maintenance treatment of ulcerative colitis with Azulfidine should be continued indefinitely unless contraindicated by side effects. Observe patients carefully, since in many cases adjustment of dosage will control side effects (see Prescribing Information). Azulfidine is also available in enteric-coated EN-tab® tablet form for those patients susceptible to gastric upset.

Over the long haul the best preventative is the proven safety of continuing maintenance treatment.

*Reprint available from Pharmacia.

AZULFIDINE®

(sulfasalazine, N.F.)

Simulated flares on a pipeline intended to represent acute exacerbation of chronic ulcerative colitis.

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AZULFIDINE®
(sulfasalazine, N.F.)
Tablets and EN-tabs®

INDICATIONS: AZULFIDINE (sulfasalazine, N.F.) is indicated in the treatment of mild to moderate ulcerative colitis, and as adjunctive therapy in severe ulcerative colitis. AZULFIDINE EN-tabs are particularly indicated in patients who experience gastrointestinal intolerance after the first few doses of the drug, when such intolerance is not primarily due to high blood levels of sulfapyridine and its metabolites and in those for whom a reduction in dosage does not alleviate the gastrointestinal effects.
CONTRAINDICATIONS: Hypersensitivity to sulfonamides or salicylates. In infants under 2 years. Intestinal and urinary obstruction. Pregnancy at term and during the nursing period. In patients with porphyria.
WARNINGS: The safe use of sulfonamides in pregnancy has not been established. Evaluate benefit to risk carefully when giving sulfonamides during pregnancy, especially at term, since kernicterus may be produced in the newborn. The teratogenic potential of most sulfonamides has not been thoroughly investigated in any species and a significant increase of cleft palate and other bony abnormalities has been observed when certain sulfonamides were given orally to pregnant rats and mice at 7 to 25 times the human therapeutic dose.
Deaths associated with the administration of AZULFIDINE (sulfasalazine, N.F.) have been reported from hypersensitivity reactions, agranulocytosis, aplastic anemia, other blood dyscrasias, renal and liver damage, irreversible neuromuscular and CNS changes and fibrosing alveolitis.
The presence of clinical signs such as sore throat, fever, pallor, purpura, or jaundice may be indications of serious blood disorders.
Complete blood counts as well as urinalysis with microscopic examination should be done frequently.
PRECAUTIONS: Administer with caution to patients with impaired renal or hepatic function, severe allergy or bronchial asthma.
Patients with glucose-6-phosphate dehydrogenase deficiency should be observed closely for signs of hemolytic anemia.
Maintain adequate fluid intake to prevent crystalluria and stone formation.
ADVERSE REACTIONS: Adverse reactions have been observed in 5 to 55% of patients included in clinical studies reported in the literature. Experience suggests that with daily dosages of 4 g or more, adverse reactions tend to increase. The most common adverse reactions associated with AZULFIDINE therapy are anorexia, nausea, vomiting, and gastric distress. The following adverse reactions have been reported to occur during therapy with AZULFIDINE.
Blood dyscrasias: Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, Heinz Body anemia, purpura, hypoprothrombinemia, "cyanosis," and methemoglobinemia.
Hypersensitivity reactions: Generalized skin eruptions, erythema multiforme (Stevens-Johnson syndrome), parapsoriasis varioliformis acuta (Mucha-Haberman syndrome), exfoliative dermatitis, epidermal necrolysis (Lyell's syndrome) with corneal damage, pruritus, urticaria, photosensitization, anaphylaxis, serum sickness syndrome, chills, drug fever, periorbital edema, conjunctival and scleral injection, arthralgia, transient pulmonary changes with eosinophilia and decreased pulmonary function, allergic myocarditis, polyarteritis nodosa, and L.E. phenomenon.
Gastrointestinal reactions: Anorexia, nausea, emesis, abdominal pains, diarrhea, bloody diarrhea, impaired folic acid and digoxin absorption, stomatitis, pancreatitis, and hepatitis.
CNS reactions: Headache, vertigo, tinnitus, hearing loss, peripheral neuropathy, transient lesions of posterior spinal column, transverse myelitis, ataxia, convulsions, insomnia, mental depression, hallucinations and drowsiness.
Renal reactions: Crystalluria, hematuria, proteinuria, and nephrotic syndrome. Toxic nephrosis with oliguria and anuria.
Incidents of alopecia and reduction in sperm count and viability have also been reported.
The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides), and oral hypoglycemic agents. Goiter production, diuresis, and hypoglycemia have occurred rarely in patients receiving sulfonamides. Cross sensitivity may exist with these agents.
AZULFIDINE (sulfasalazine, N.F.) produces an orange-yellow color when the urine is alkaline. Similar discoloration of the skin has also been reported.
SUPPLIED: Tablets and EN-tabs (enteric-coated) 0.5 gm, in bottles of 100 and 500. Also available as Azulfidine Unit Dose in boxes of 100's and 1000's.
IMPORTANT: See full prescribing information before administering AZULFIDINE.

References:
1. Dissanayake, A.S. and Truelove, S.C.: Gut 14:923-926, Dec. 1973.
2. Bargen, J.A.: Amer. Surg. 28:630-637, Sept. 1962.
3. Hightower, N.C., Jr., et al.: Amer. J. Digest. Dis. 3:722-733, 861-876, 931-941, Oct., Nov., Dec. 1958.
4. Roth, J.L.A.: Chapter 69, in Bockus, H. (ed.): Gastroenterology, Vol. II. W.B. Saunders Company.
5. Riis, P., et al.: Scand. J. Gastroenterol. 8:71-74, 1973.
6. Goldstein, F. and Thornton, J.J.: Consultant 14:96-103, July 1974.

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MEETINGS OF INTEREST

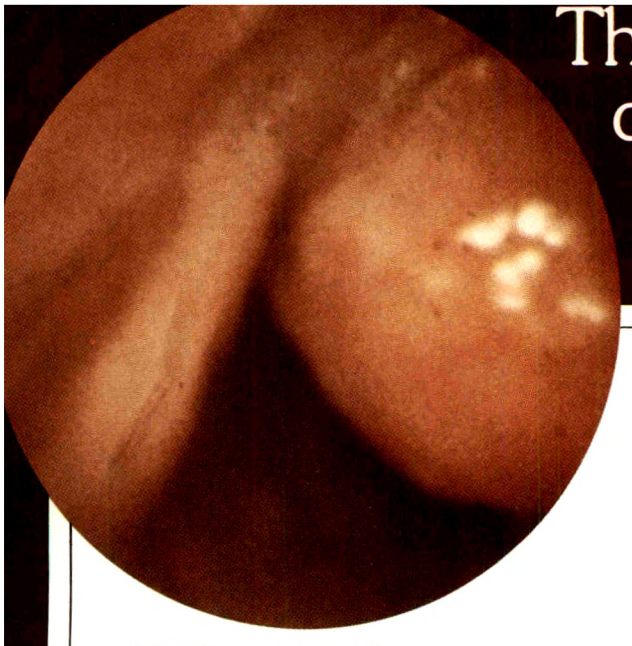
44th Annual Convention, American College of Gastroenterology, Disneyland Hotel, Anaheim, CA, 22-24 October 1979.

Annual Course in Postgraduate Gastroenterology, American College of Gastroenterology, Disneyland Hotel, Anaheim, CA, 25-27 October 1979.

Portal Hypertension and Its Complications—Update. Postgraduate Course of the American Association for the Study of Liver Disease, Chicago, IL, 7-8 November 1978.

One Day of Gastroenterology, Postgraduate Course co-sponsored by the American College of Gastroenterology, the Southern Medical Association. Georgia World Congress Center, Atlanta, GA, 11 November 1978.

International Conference on Digestive Diseases, Postgraduate Course co-sponsored by the American College of Gastroenterology, the University of South Florida Medical School in Tampa and the Florida Hospital in Orlando. Dutch Inn, Lake Buena Vista, FL, 28-30 January 1979.



The patient has dysphagia of 1½ years' duration.

Physical exam is unrevealing.
X-ray studies are inconclusive.

What is the diagnosis?

Esophagoscopy resolves the question.

A 56-year-old man was seen because of increasingly severe dysphagia of one and a half years' duration. At the time of admission, the patient could take only liquids. Physical examination was unrevealing.

A filling defect of the midesophagus was observed by the radiologist. On several projections it appeared to be extrinsic, although an intrinsic lesion, such as leiomyoma, could not be excluded.

Esophagoscopy was performed, and a round submucosal tumor thought to be a *leiomyoma* was identified at the level of 28 cm from the incisor teeth. The patient refused surgical intervention.

Causes of dysphagia may include esophageal carcinoma, achalasia, lower esophageal ring or esophageal web, as well as benign neoplasm. Benign tumors are rare and when detected are usually only incidental findings. Such tumors may, however, become symptomatic upon reaching a large enough size. Such tumors are most often *leiomyomas*, which can partially obstruct the esophageal lumen. Characteristically, they develop central ulceration and hemorrhage.

Case discussion based on *The Clinical Significance of Esophagoscopy* by Bernard M. Schuman, M.D., one in a series of monographs made available by Roche Laboratories in fulfillment of its commitment to continuing education in gastroenterology. This case history illustrates the diagnostic use of endoscopy; it does not represent an indication for Librax therapy.

Endoscopy

-confirmatory or contradictory-

a valuable aid in the diagnosis of G.I. disorders

The development of highly specialized fiberoptic endoscopes has significantly enhanced the accuracy and efficiency of gastrointestinal diagnosis and treatment. Frequently, when both x-ray and laboratory tests have been repeatedly negative, endoscopy has uncovered an organic lesion.

Whether a G.I. condition is eventually confirmed as functional or organic, every patient should receive a thorough examination of his emotional profile and life stresses; such factors may give rise to the patient's symptomatic complaints or aggravate the symptoms of an organic disorder.

Librax®: a valuable aid in the treatment of irritable bowel syndrome*

The diagnosis of irritable bowel syndrome is based on the patient's symptoms and history, plus the exclusion of an organic disorder. In this condition, Librax has been found doubly valuable as an adjunct to reassurance and counseling because it relieves distressing symptoms of both emotional and somatic origin.

1 **Only Librax provides the specific antianxiety action of Librium®** (chlordiazepoxide HCl), in addition to the antisecretory-antispasmodic actions of Quarzan® (clidinium Br)—both original developments of Roche research.

2 **Librax seldom impairs mental acuity or performance** when given in proper dosage. However, as with all preparations containing CNS-acting agents, patients should be cautioned against hazardous occupations requiring complete mental alertness.

3 **Flexibility of dosage helps meet varying requirements:** 1 or 2 capsules three or four times daily, before meals and at bedtime.

4 **The convenience and economy of a single Rx** help sustain patient compliance, while providing relief of both emotional and somatic symptoms.

A distinctive antianxiety-antispasmodic agent

Librax®

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium Br.

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*Librax has been evaluated as possibly effective for this indication.
Please see brief summary of prescribing information on following page.

Librax®

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium Br.

Please consult complete prescribing information, a summary of which follows:

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows: "Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Physical and psychological dependence rarely reported on recommended doses, but use caution in administering Librium® (chlordiazepoxide HCl) to known addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions) reported following discontinuation of the drug.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.**

As with all anticholinergics, inhibition of lactation may occur.

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established.

Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.

Dosage: Individualize for maximum benefit. Usual maintenance dose is 1-2 capsules, 3-4 times/day, before meals and at bedtime. Geriatric patients—see Precautions.

How Supplied: Available in green capsules, each containing 5 mg chlordiazepoxide HCl (Librium®) and 2.5 mg clidinium Br (Quarzan®)—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 50, singly and in trays of 10.

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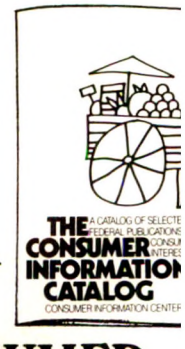
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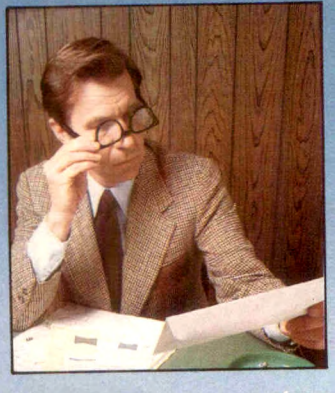
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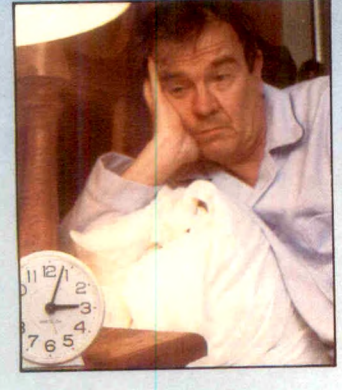
Which of these cirrhotic patients has portal-systemic encephalopathy (PSE)?

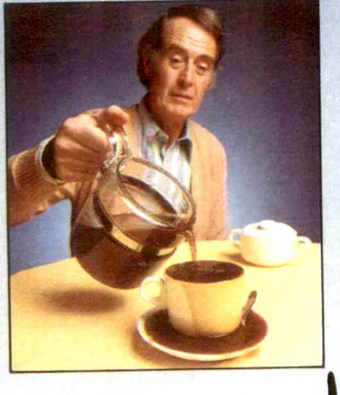
(Also called Hepatic Encephalopathy, Hepatic Coma.)

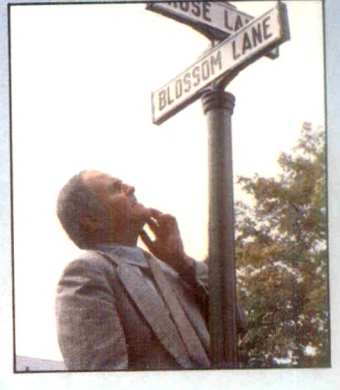












(Please turn page for answer.)

Cephulac®
(lactulose) Syrup

Brief Summary

INDICATIONS: For the prevention and treatment of portal-systemic encephalopathy, including the stages of hepatic pre-coma and coma. Controlled studies have shown that lactulose syrup therapy reduces the blood ammonia levels by 25-50%; this is generally paralleled by an improvement in the patients' mental state and by an improvement in EEG patterns. The clinical response has been observed in about 75% of patients, which is at least as satisfactory as that resulting from neomycin therapy. An increase in patients' protein tolerance is also frequently observed with lactulose therapy. In the treatment of chronic portal-systemic encephalopathy, Cephulac has been given for over 2 years in controlled studies.

CONTRAINDICATIONS: Since Cephulac contains galactose (less than 2.2 g./15 ml.), it is contraindicated in patients who require a low galactose diet.

WARNINGS: *Use in Pregnancy:* Studies in laboratory animals have not revealed a teratogenic potential of lactulose. The safety of lactulose syrup during pregnancy and its effect on the mother or the fetus have not been evaluated in humans. The physician and patient should understand that the possibility that lactulose syrup might cause damage to the human fetus cannot be excluded. Lactulose syrup should not be given during pregnancy unless, in the opinion of the physician, the possible benefits outweigh the possible risks.

PRECAUTIONS: Lactulose syrup contains galactose (less than 2.2 g./15 ml.) and lactose (less than 1.2 g./15 ml.) and it should be used with caution in diabetics. There have been conflicting reports about the concomitant use of neomycin and lactulose syrup. Theoretically, the elimination of certain colonic bacteria by neomycin and possibly other anti-infective agents may interfere with the desired degradation of lactulose and thus prevent the acidification of colonic contents. Thus the status of the lactulose-treated patient should be closely monitored in the event of concomitant oral anti-infective therapy. Other laxatives should not be used especially during the initial phase of therapy for portal-systemic encephalopathy because the loose stools resulting from their use may falsely suggest that adequate Cephulac dosage has been achieved. In the overall management of portal-systemic encephalopathy it should be recognized that there is serious underlying liver disease with complications such as electrolyte disturbance (e.g., hypokalemia) for which other specific therapy may be required.

ADVERSE REACTIONS: Cephulac may produce gaseous distention with flatulence or belching and abdominal discomfort such as cramping in about 20% of patients. Excessive dosage can lead to diarrhea. Nausea and vomiting have been reported infrequently.

DOSAGE AND ADMINISTRATION: The usual dosage is 2 to 3 tablespoonfuls (30 to 45 ml., containing 20 g. to 30 g. of lactulose) three or four times daily. The dosage may be adjusted every day or two to produce 2 or 3 soft stools daily. Hourly doses of 30 to 45 ml. of Cephulac may be used to induce the rapid laxation indicated in the initial phase of the therapy of portal-systemic encephalopathy. When the laxative effect has been achieved, the dose of Cephulac may then be reduced to the recommended daily dose. Improvement in the patient's condition may occur within 24 hours but may not begin before 48 hours or even later. Continuous long-term therapy is indicated to lessen the severity and prevent the recurrence of portal-systemic encephalopathy. The dose of Cephulac for this purpose is the same as the recommended daily dose.

Product Information as of August, 1975

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7-3292(Y366A)

43rd Annual Convention of the American College of Gastroenterology and Course in Postgraduate Gastroenterology

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The Marriott, Denver, Colo.
24-30 September 1978

this is portal-systemic encephalopathy (PSE)–

(Also called Hepatic Encephalopathy, pre-Hepatic Coma)

a common complication of chronic liver disease.

Suspect PSE in every patient with cirrhosis.

Common early symptoms

- irritability
- euphoria
- lack of concern for others
- inappropriate behavior
- faraway look
- inversion of sleep pattern

Results of recent investigations of PSE

- Two-thirds of cirrhotic patients with portal hypertension who appeared mentally normal by conventional assessment revealed impairment of cerebral function on psychomotor testing. This dysfunction was in the same range as that in patients with brain damage after blunt trauma.[1]
- Alcoholic males with cirrhosis demonstrated a mental state significantly inferior to alcoholics without cirrhosis.[2]
- The majority of cirrhotic patients with portacaval shunts who appeared mentally normal had demonstrable psychomotor impairment.[3]

Treat PSE with Cephulac (lactulose) Syrup

- relieves PSE in 75% of episodes
- acts without serious adverse reactions
- lowers blood ammonia levels
- improves EEG and mental state
- permits more normal dietary protein intake
- provides an easy-to-manage means of long-term therapy

Cephulac®

(lactulose) Syrup

Each 15 ml. of syrup contains: 10 g. lactulose (and less than 2.2 g. galactose, less than 1.2 g. lactose, and 1.2 g. or less of other sugars)

for the prevention and treatment of PSE in your patients with chronic liver disease

Merrell MERRELL-NATIONAL LABORATORIES
Division of Richardson-Merrell Inc
Cincinnati, Ohio 45215

Brief Summary

INDICATIONS: For the prevention and treatment of portal-systemic encephalopathy, including the stages of hepatic pre-coma and coma. Controlled studies have shown that lactulose syrup therapy reduces the blood ammonia levels by 25-50%; this is generally paralleled by an improvement in the patients' mental state and by an improvement in EEG patterns. The clinical response has been observed in about 75% of patients, which is at least as satisfactory as that resulting from neomycin therapy. An increase in patients' protein tolerance is also frequently observed with lactulose therapy. In the treatment of chronic portal-systemic encephalopathy, Cephulac has been given for over 2 years in controlled studies.

CONTRAINDICATIONS: Since Cephulac contains galactose (less than 2.2 g./ 15 ml.), it is contraindicated in patients who require a low galactose diet.

WARNINGS: *Use in Pregnancy*: Studies in laboratory animals have not revealed a teratogenic potential of lactulose. The safety of lactulose syrup during pregnancy and its effect on the mother or the fetus have not been evaluated in humans. The physician and patient should understand that the possibility that lactulose syrup might cause damage to the human fetus cannot be excluded. Lactulose syrup should not be given during pregnancy unless, in the opinion of the physician, the possible benefits outweigh the possible risks.

PRECAUTIONS: Lactulose syrup contains galactose (less than 2.2 g./ 15 ml.) and lactose (less than 1.2 g./ 15 ml.) and it should be used with caution in diabetics. There have been conflicting reports about the concomitant use of neomycin and lactulose syrup. Theoretically, the elimination of certain colonic bacteria by neomycin and possibly other anti-infective agents may interfere with the desired degradation of lactulose and thus prevent the acidification of colonic contents. Thus the status of the lactulose-treated patient should be closely monitored in the event of concomitant oral anti-infective therapy. Other laxatives should not be used especially during the initial phase of therapy for portal-systemic encephalopathy because the loose stools resulting from their use may falsely suggest that adequate Cephulac dosage has been achieved. In the overall management of portal-systemic encephalopathy it should be recognized that there is serious underlying liver disease with complications such as electrolyte disturbance (e.g., hypokalemia) for which other specific therapy may be required.

ADVERSE REACTIONS: Cephulac may produce gaseous distention with flatulence or belching and abdominal discomfort such as cramping in about 20% of patients. Excessive cosage can lead to diarrhea. Nausea and vomiting have been reported infrequently.

DOSAGE AND ADMINISTRATION: The usual dosage is 2 to 3 tablespoonfuls (30 to 45 ml., containing 20 g. to 30 g. of lactulose) three or four times daily. The dosage may be adjusted every day or two to produce 2 or 3 soft stools daily. Hourly doses of 30 to 45 ml. of Cephulac may be used to induce the rapid laxation indicated in the initial phase of the therapy of portal-systemic encephalopathy. When the laxative effect has been achieved, the dose of Cephulac may then be reduced to the recommended daily dose. Improvement in the patient's condition may occur within 24 hours but may not begin before 48 hours or even later. Continuous long-term therapy is indicated to lessen the severity and prevent the recurrence of portal-systemic encephalopathy. The dose of Cephulac for this purpose is the same as the recommended daily dose.

Product Information as of August, 1975

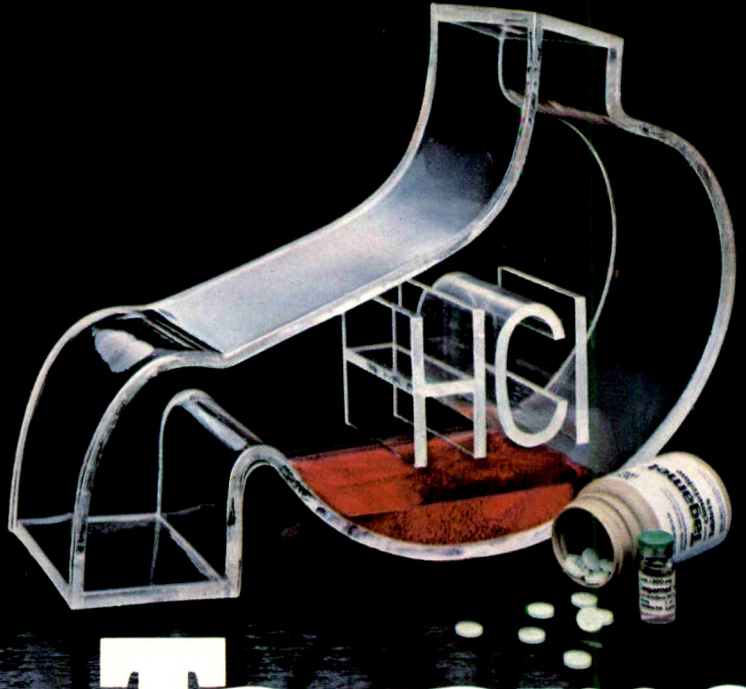
References:

1. Schomerus, H. and Hamster, W.: Latent portasystemic encephalopathy. Digestion 14:548-549, 1976.
2. Smith, H.H. and Smith, L.S.: WAIS functioning of cirrhotic and non-cirrhotic alcoholics. J. Clin. Psychol. 33:309-313, 1977.
3. Rikkers, L., Jenko, P., Rudman, D. and Freides, D.: Subclinical hepatic encephalopathy: detection, prevalence, and relationship to nitrogen metabolism. Gastroenterology 72:1119, 1977.

8-3527 (Y451A)



Significant gastric acid suppression means effective duodenal ulcer therapy



Tagamet®

brand of cimetidine

Tablets, 300 mg. Injection, 300 mg./2 ml

The H_2 Receptor Antagonist

Working directly at the parietal cell, 'Tagamet' suppresses gastric acid secretion after meals and throughout the night, producing important patient benefits:

●

rapid ulcer healing

●

effective symptom relief, day and night

In *Duodenal Ulcer,* the recommended dosage is 300 mg. four times a day, with meals and at bedtime. Treatment periods should not exceed eight weeks.

While healing may occur during the first week or two, 'Tagamet' therapy should be continued for four to six weeks unless healing has been demonstrated endoscopically.

In *Pathological Hypersecretory Disorders,* the dosage is also 300 mg. four times a day, with meals and at bedtime. In some patients it may be necessary to administer 'Tagamet' 300 mg. doses more frequently (not to exceed 2400 mg. per day) and continue as long as clinically indicated.

Dosage should be reduced in patients with impaired renal function.

Concomitant antacids should be given as needed for relief of pain.

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

Indications: 'Tagamet' (brand of cimetidine) is indicated in the short-term (up to 8 weeks) treatment of duodenal ulcer; and in the treatment of pathological hypersecretory disorders (i.e., Zollinger-Ellison syndrome, systemic mastocytosis and multiple endocrine adenomas). Concomitant antacids should be given as needed for relief of pain. Studies to date do not provide evidence of the safety of cimetidine in uncomplicated duodenal ulcer beyond 8 weeks.

Contraindications: There are no known contraindications to the use of 'Tagamet'.

Precautions: In a 24-month toxicity study in rats at dose levels approximating 9 to 56 times the recommended human dose, benign Leydig cell tumors were seen. These were common in both the treated and control groups, and the incidence became significantly higher only in the aged rats receiving 'Tagamet'. Reproduction studies in animals have shown no evidence of impaired mating performance or fertility.

Lack of experience to date precludes recommending 'Tagamet' for use in pregnant patients, women of childbearing potential, nursing mothers or children under 16 unless anticipated benefits outweigh potential risks; generally, nursing should be discontinued in patients taking the drug.

Adverse Reactions: Diarrhea, muscular pain, dizziness, rash, mild gynecomastia. A few cases of neutropenia have been reported, but no causal relationship could be established. Small, regularly observed, reversible increases in plasma creatinine and some increases in serum transaminase have been reported.

How Supplied: Pale Green Tablets: 300 mg. tablets in bottles of 100 and Single Unit Packages of 100 (intended for institutional use only).

Injection: 300 mg./2 ml. in single-dose vials in packages of 10.

Date of issuance Sept. 1977

SK&F LAB CO., Carolina, P.R. 00630

Tagamet®
brand of
cimetidine

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disposable unit-dose
hydrocortisone retention enema

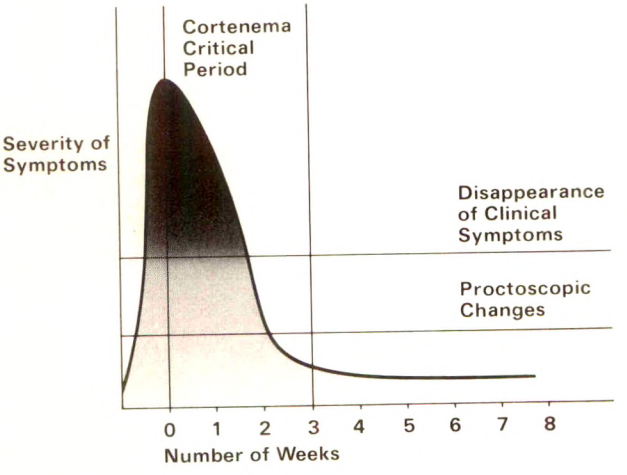
COMPOSITION: Each 60 ml. unit contains Hydrocortisone, 100 mg. in an aqueous solution of carboxypolymethylene, polysorbate 80, and methy paraben, 0.18% as a preservative.
INDICATIONS: Adjunctive therapy in ulcerative colitis; especially distal ulcerative proctitis, proctosigmoiditis, left-sided colitis; proved useful also in some cases involving transverse and ascending colons.
CONTRAINDICATIONS: Systemic fungal infections; recent ileocolostomy.
WARNINGS: In severe ulcerative colitis, avoid delay of needed surgery pending response to medical therapy. Careful insertion of enema tip is advisable to avoid rectal wall damage. Observe warnings of corticosteroid use; increase dosage of rapid-acting corticosteroids in unusual stress; corticosteroids may mask and decrease resistance to infection; prolonged use may predispose to cataracts, glaucoma, secondary ocular infections.
Usage in pregnancy: Pending adequate studies, corticosteroid use in pregnant, lactating or potentially childbearing women requires weighing possible drug benefits against potential hazards to mother and progeny. After large corticosteroid doses during pregnancy, observe neonates for hypoadrenalism.
Hydrocortisone or cortisone therapy may increase blood pressure, sodium and water retention, potassium excretion—effects less likely with synthetic derivatives, except in high doses. Salt restriction and potassium supplementation may be needed. All corticosteroids increase calcium excretion.
Avoid immunization procedures, including smallpox vaccination, during corticosteroid therapy, because of possible neurologic complications and lack of antibody response. Observe corticosteroid-treated patients with latent tuberculosis or tuberculin reactivity for signs of reactivated disease; provide chemoprophylaxis during prolonged corticosteroid dosage.
PRECAUTIONS: Use CORTENEMA cautiously in probability of bowel perforation, abscess or pyogenic infection, new anastomoses, obstruction, extensive fistulas or sinus tracts, and in peptic ulcer, diverticulitis, renal insufficiency, hypertension, osteoporosis and myasthenia gravis. Minimize hazard of adrenocortical insufficiency after prolonged treatment, by reducing dosage gradually and by adding mineralocorticoid and glucocorticoid support in post-treatment stress situations. In surgical infections during corticosteroid therapy, consider increasing antimicrobial dosage.
Use corticosteroids cautiously in hypothyroidism, cirrhosis and ocular herpes simplex; use aspirin cautiously with corticosteroids in hypoprothrombinemia. Psychic derangements may appear and emotional instability or psychotic tendencies may be aggravated with corticosteroid use. Carefully monitor growth of children on long-term corticosteroid therapy. Use the lowest effective corticosteroid dosage and reduce it gradually when possible.
ADVERSE REACTIONS: Local pain or burning, and rectal bleeding attributed to CORTENEMA have been reported rarely. Apparent exacerbations or sensitivity reactions also occur rarely. The following adverse reactions should be kept in mind whenever corticosteroids are given by rectal administration:
Fluid and Electrolyte Disturbances: Sodium retention; fluid retention; congestive heart failure in susceptible patients; potassium loss; hypokalemic alkalosis; hypertension. *Musculoskeletal:* Muscle Weakness; steroid myopathy; loss of muscle mass; osteoporosis; vertebral compression fractures; aseptic necrosis of femoral and humeral heads; pathologic fracture of long bones. *Gastrointestinal:* Peptic ulcer with possible perforation and hemorrhage; pancreatitis; abdominal distention; ulcerative esophagitis. *Dermatologic:* Impaired wound healing; thin fragile skin; petechiae and ecchymoses; facial erythema; increased sweating; may suppress reactions to skin tests. *Neurologic:* Convulsions; increased intracranial pressure with papilledema (pseudo-tumor cerebri) usually after treatment; vertigo; headache. *Endocrine:* Menstrual irregularities; development of Cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetics. *Ophthalmic:* Posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos. *Metabolic:* Negative nitrogen balance due to protein catabolism.
DOSAGE AND ADMINISTRATION: CORTENEMA should be used adjunctively with such supportive measures as dietary control, sedatives, antidiarrheal and antibacterial agents and blood replacement. The usual dosage, administered intrarectally in the evening before retiring, is 1 CORTENEMA per day for 2-3 weeks and every other evening thereafter until clinical and proctologic remission occur. CORTENEMA should be retained at least 1 hour or, preferably, all night and may be facilitated by prior sedative or antidiarrheal medication. Duration of treatment depends on both clinical and proctologic response. Clinical symptoms usually subside within 3-5 days; mucosal improvement may require longer, up to 2-3 months. Discontinue CORTENEMA if improvement fails to occur within 3 weeks.
HOW SUPPLIED: Single-dose 60-cc. bottles, in packages of 1 or 7, with instructions for patients.

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BAUDETTE, MINN. 56623

The first three weeks of therapy... that's when you most need:

Cortenema®

disposable unit-dose hydrocortisone retention enema



Once a diagnosis is established, Cortenema often is the only medication required for treatment of mild to moderate distal ulcerative colitis, characterized by rectal bleeding, stool abnormality (diarrhea or constipation), and diffuse mucosal ulceration and friability limited to the rectum or rectosigmoid colon.

Progress of signs and symptoms

Inflammation, bleeding and tenesmus usually start to subside within three to five days. Sigmoidoscopic examination after two or three weeks will reveal extent of mucosal improvement and direct subsequent therapy. (Severe cases may require up to three months Cortenema treatment followed by gradually reduced doses until discontinuation.)

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Cortenema is unit-dosed, ready to administer, disposable. Available in packages of one or seven.

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Hydrocortisone enema therapy provides relief of symptoms and mucosal inflammation with minimal concern for steroid side effects. About 30%-50% absorption may occur, but with only transient adrenal suppression reported. Therapy is economical for the patient. The usual three week course costs far less than even one day of hospitalized treatment.



Originators of hydrocortisone enema therapy.

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See page opposite for brief summary.

in irritable colon*

When stress makes waves for the spasm reactor...

A normal reaction to emotional stress is a marked increase in both the strength and frequency of wave-like contractions of colonic motility.[1] However, in the patient with irritable bowel syndrome, this psychovisceral reaction is of greater intensity and duration than normal.[2]

The result can be G.I. spasm.

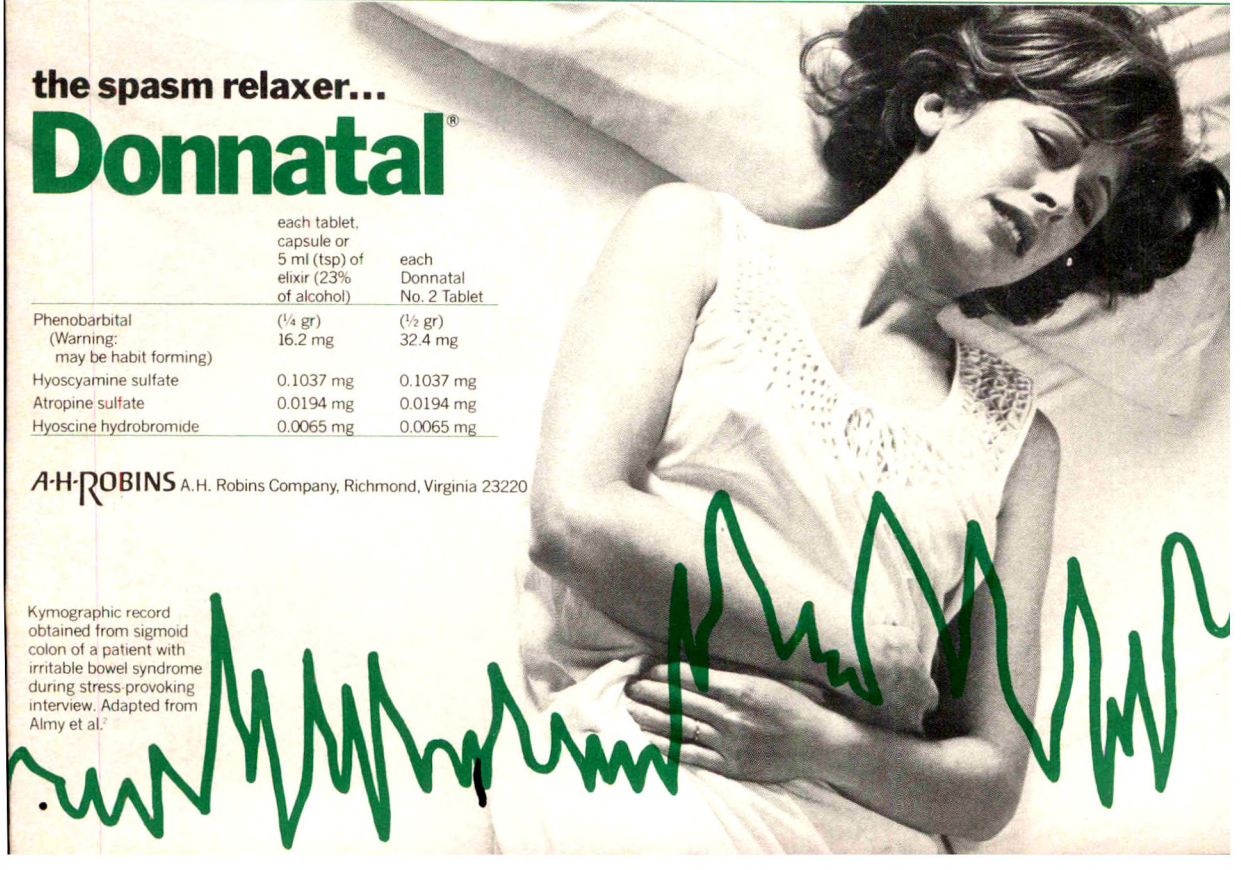
When spasm and pain associated with irritable bowel syndrome call for treatment beyond your counseling and reassurance, Donnatal may prove to be a helpful adjunct. The smooth central sedation and prompt peripheral antispasmodic/anticholinergic action of Donnatal may provide this symptomatic relief necessary to help calm the waves ...and quell the spasm.

References: 1. Almy, T.P., Kern, F., and Tulin, M.: Alterations in colonic function in man under stress. II: Experimental production of sigmoid spasm in healthy persons. *Gastroenterology* 12(3):425-436, 1949. **2.** Almy, T.P., Hinkle, L.E., Berle, B., et al.: Alterations in colonic function in man under stress. III: Experimental production of sigmoid spasm in patients with spastic constipation. *Gastroenterology* 12(3):437-449, 1949.

*Indications: Based on a review of this drug by the NAS/NRC and/or other information, FDA has classified the following indications as possibly effective: adjunctive therapy in the treatment of peptic ulcer; the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

Final classification of the less-than-effective indications requires further investigation.

Contraindicated in patients with glaucoma, renal or hepatic disease, obstructive uropathy (for example, bladder neck obstruction due to prostatic hypertrophy), or a hypersensitivity to any of the ingredients. Blurred vision, dry mouth, difficult urination, and flushing or dryness of the skin may occur at higher dosage levels, rarely at the usual dosage.



the spasm relaxer...

Donnatal®

	each tablet, capsule or 5 ml (tsp) of elixir (23% of alcohol)	each Donnatal No. 2 Tablet
Phenobarbital (Warning: may be habit forming)	(¼ gr) 16.2 mg	(½ gr) 32.4 mg
Hyoscyamine sulfate	0.1037 mg	0.1037 mg
Atropine sulfate	0.0194 mg	0.0194 mg
Hyoscine hydrobromide	0.0065 mg	0.0065 mg

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Kymographic record obtained from sigmoid colon of a patient with irritable bowel syndrome during stress-provoking interview. Adapted from Almy et al.[2]

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Inhibition by Propranolol of Bile Acid- and PGE_1-stimulated cAMP and Intestinal Secretion

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Three colonic and three ileal loops were prepared in six rabbits pretreated with propranolol (PR) 4 mg./kg. I.V. and in five untreated rabbits. In random order, 1 ml. of either deoxycholic acid (DCA) 6 mM., prostaglandin E_1 (PGE_1) 20 μg./ml., or saline was placed in each colonic loop and 1 ml. of either cholera enterotoxin (CE) 10 μg./ml., PGE_1 20 μg./ml., or saline was placed in each ileal loop. In untreated animals, DCA and PGE_1 in the colon and CE and PGE_1 in the ileum stimulated ($P < 0.01$) adenylate cyclase (AC) and net secretion. In the colon, PR abolished DCA-stimulation of AC and net secretion and decreased PGE_1-stimulated AC ($P < 0.01$) and net secretion. In conclusion, at the doses and times studied, colonic-AC and net secretion stimulated by PGE_1 or DCA was distinguished from small bowel-AC and net secretion stimulated by PGE_1 or CE.

INTRODUCTION

We reported previously that propranolol (PR) inhibits deoxycholic acid (DCA)-stimulation of colonic adenylate cyclase (AC) and net fluid secretion and has no effect on cholera enterotoxin (CE)-stimulation of small bowel AC and secretion.[1] That study, however, did not discern whether PR is a general inhibitor of colonic AC or is specific for DCA-stimulated colonic AC or if PR effects other stimulants of ileal or colonic AC. Prostaglandin-E_1 (PGE_1) stimulates AC and secretion in the small bowel of animals[2, 3] and man,[4] but its effect on colonic AC, phosphodiesterase (PDE) and secretion are not known. This study was designed, therefore, to investigate the agent- or site-specificity of PR-inhibition of cyclic-AMP-mediated intestinal secretion.

From the Department of Gastroenterology, Cedars-Sinai Medical Center and the University of California at Los Angeles School of Medicine.
Supported in part by NIH Grant #AM 15631.

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The aims, accordingly, were to determine if PGE_1 stimulates colonic AC and net secretion and whether these actions of PGE_1 in the colon and small bowel are inhibited by PR.

Methods

Preparation of colonic loops:—Female New Zealand white rabbits, raised in a laboratory environment, fed Purina rabbit chow until 12 weeks of age and weighing 2.2 ± 0.3 kg., were used in all experiments. The rabbits were fasted for 48 hours before operation. To standardize a possible diurnal variation of cAMP or AC activity the animals were operated on at 8 A.M. and were killed at 1 P.M. of the same day.

At operation the peritoneal space was entered through an anterior mid line abdominal incision using local anesthesia (1% lidocaine). Ten milliliters of 0.9% NaCl, pH 7.5, were injected into both the colon and the ileum, distal to a ligature, to cleanse that intestinal segment of its contents. Colonic and ileal loops were constructed using the technic described by Forth, et al.[5] The loops were doubly ligated and separated by 0.5-1.0 cm. from one another.

Experimental design:—Three loops (average length 5.8 ± 0.4 cm.) in the ascending colon and three loops (average length 5.4 ± 0.3 cm.) in the distal ileum were constructed in each of 11 rabbits. Six of the animals were treated intravenously with PR, 4 mg./kg. ½ hour before loop construction; five control rabbits did not receive pretreatment with PR. In random order, 1 ml. of either DCA 6 mM., PGE_1 20 μg./ml., or saline was placed in each colonic loop and 1 ml. of CE 10 μg./ml., PGE_1 20 μg./ml., or saline was placed in each ileal loop. The animal was killed five hours later by an air embolus into a marginal ear vein. Then, mucosal AC and PDE activities and the luminal fluid volumes in each loop were measured.

The volume of fluid and the length of each loop were recorded to express results in milliliters net secretion per centimeter of intestine. The volume of fluid in each loop was measured after making a small incision adjacent to the suture ligature and gently expressing the contents of the loop through the incisional orifice into a graduated centrifuge tube. The use of randomized orders and control loops in this experimental design obviates any potential interfering effects of the multiple ligations. The Student "t" test and unpaired analyses were used to obtain P values.

AC catalyzes the formation of cAMP from adenosine triphosphate (ATP) within the cell. PDE hydrolyzes the 3′,5′-phosphate bond of cAMP forming 5′-AMP, an inactive compound. The cAMP content, therefore, is the result of the relative activities of AC and PDE. AC activity was assayed in the mucosa of all intestinal loops (n = 66) of the five control rabbits (30 loops) and of the six pretreated rabbits (36 loops). PDE was assayed in the colonic loops of all animals and in the ileal loops of two animals. CE[6, 7] and PGE_1[8] in the same concentrations used in this experiment previously have been shown not to affect PDE in the ileum.

Preparation of tissue for enzyme assay:—After recording the volume of secretion, each loop was individually opened by a longitudinal incision. The mucosa was carefully separated from the muscularis and was immediately placed in ice-cold buffer (0.05 M Tris-HCl, pH 7.5). The mucosa then was rapidly minced and homogenized by six strokes of an ice-cold, hand-driven, conical, Kontes glass tissue-homogenizer and strained through gauze. The time from initiation of mucosal stripping to homogenization was five minutes. Light

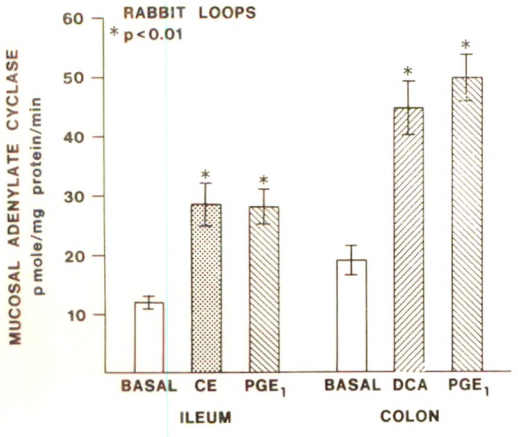


Fig. 1—Effect of CE, PGE_1 and DCA on mucosal AC in ileum and colon. CE significantly ($P < 0.01$) stimulated AC in the ileum; DCA significantly ($P < 0.01$) stimulated AC in the colon; PGE_1 significantly ($P < 0.01$) stimulated AC in ileum and colon.

microscopic examination of coded intestinal specimens revealed normal morphology after all treatments.

For the AC assay the homogenate was centrifuged at 10,000 × g for 10 minutes at 0° C.[9] The pellet was washed twice by resuspending in buffer and was used immediately for the AC assay. Bile acids were not detectable in the pellet by gas-liquid chromatography at a sensitivity able to detect 0.5×10^{-9} M.[10] Thus the AC activity in the washed pellet does not reflect the action of retained bile acids. For the PDE assay the homogenate was centrifuged at 30,000 × g for 10 minutes and enzyme activity was determined in the supernatant. The quantity of mucosal protein in each assay was determined by the Folin and Cioalteu phenol reagent method.[11]

Adenylate cyclase assay:—The method used for determination of AC in tissue combines the incubation system described by Drummond and Duncan[12] and silica paper chromatography described by Woods and Waitzman.[13] The assay was performed at conditions of time (10 min.) and protein concentration (0.3 mg.) shown to be optimal in our laboratory for rabbit colonic mucosal tissue.[14] cAMP production was linear up to 15 minutes using 0.2-6.0 mg. of protein per assay. The method depends on the amount of 8-^{14}C cAMP formed after incubation of 8-^{14}C ATP with the mucosal homogenate.

The assay system in a volume of 150 μl. per vessel consisted of: 40 mM Tris-HCl (ph 7.5), 4 mM theophylline, 4 mM $MgSO_4$, 0.4 mM ATP, 130 μg./ml. of pyruvate kinase, and 0.23 μc. of 8-^{14}C-ATP tetrasodium salt (specific activity 46.7 mc. per mmole). The assay tubes were equilibrated at 37° C for two minutes. The reaction then was initiated by the addition of 50 μl. of suitably diluted tissue and the incubation was carried out for 10 minutes at 37° C. The reaction was terminated by placing the tube in a boiling bath for three minutes. Denatured protein was removed by centrifugation at 2,000 rpm for 15 minutes.

An aliquot (25 μl.) of each clear supernatant was applied on a neutral silicic acid-glass fibromatrix, 1,000 nm thickness (Chromar AP-1,000, Mallinckrodt Chemical Works, St. Louis, MO). Ascending chromatography was accomplished in sandwich chambers (Brinkman Instruments, Inc., Westbury, NY) using the solvent 2-propanol:ethyl acetate:13.6 N ammonium hydroxide (55:29:16). Development time was approximately 50 minutes. The developed spots were visualized under short-wave ultraviolet light. The labeled cAMP was counted after dispersion in 10 ml. of scintillation mixture in a Searle Mark III liquid scintillation counter (G. D. Searle & Co., Des Plaines, IL). The counts were corrected for quenching and for the experimental blank consisting of the entire incubation mixture inactivated at time zero

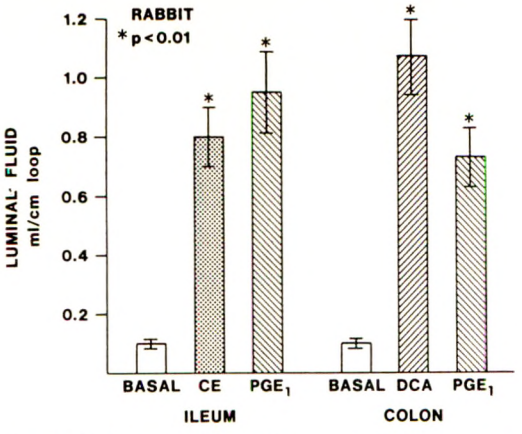


Fig. 2—Effect of CE, PGE_1 and DCA on net secretion in ileum and colon. CE significantly ($P < 0.01$) stimulated net secretion in the ileum; DCA significantly ($P < 0.01$) stimulated net secretion in the colon; PGE_1 significantly ($P < 0.01$) stimulated net secretion in the ileum and colon.

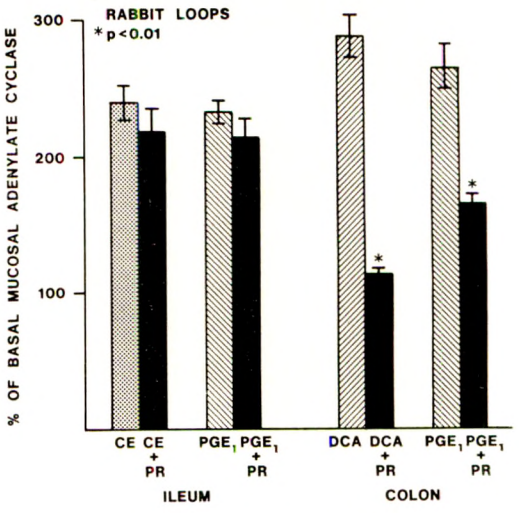


Fig. 3—Effect of PR on CE-, PGE_1- and DCA-stimulated AC in ileum and colon. PR did not affect CE- or PGE_1-stimulated AC in the ileum, completely inhibited DCA-stimulation of AC in the colon but only partially, yet significantly ($P < 0.01$) inhibited PGE_1 stimulation of AC in the colon.

by boiling. The AC activity was expressed as picomoles of cAMP formed per milligram of mucosal protein per minute and as a percentage of the control value. Each determination was performed in triplicate, which agreed within 5%.

Phosphodiesterase assay:—The activity of PDE was determined by the method of Brooker, et al[15] as modified by Kantor.[16] The method depends on hydrolysis of ^{3}H-adenosine after phosphorolysis by 5′-nucleotidase in the incubation mixture. The assay was performed at conditions of time (10 min.) and protein concentration (0.4 mg.) shown to be optimal in our laboratory for rabbit colonic mucosal tissue. cAMP degradation was linear up to 30 minutes using 0.1-0.7 mg. of protein per assay.

Fifty microliters of the supernatant obtained for PDE assay containing 0.3-0.4 mg. of protein were added to 150 μl. of incubation mixture. The final composition of the 150 μl. incubation mixture was 30 mM Tris-HCl (pH 7.5), 10mM $MgCl_2$, 0.01 mM cAMP, 0.67 mg./ml. of bovine serum albumin (BSA), 0.33 mg./ml. of 5′-nucleotidase (cobra venom) and 0.07 μc. of ^{3}H-cAMP, ammonium salt (specific activity, 38.4 Ci/mmole).

The reaction was carried out at 37° C in polyethylene scintillation vials for 10 minutes and stopped by the addition of 1 ml. of AG-1-X2 resin slurry in water (1:1). The mixture was allowed to equilibrate for 10 minutes at room temperature. Then 10 ml. of scintillation fluid were added and the activity of ^{3}H-adenosine was counted in a Searle Mark III Model 6880 liquid scintillation counter. A reaction blank for each experiment was determined in the absence of homogenate. The activity of PDE corrected for the experimental blank was expressed as the amount of cAMP hydrolyzed to 5′-AMP/mg. of protein/min. and as a percentage of the control value. Triplicate analyses agreed within 5%.

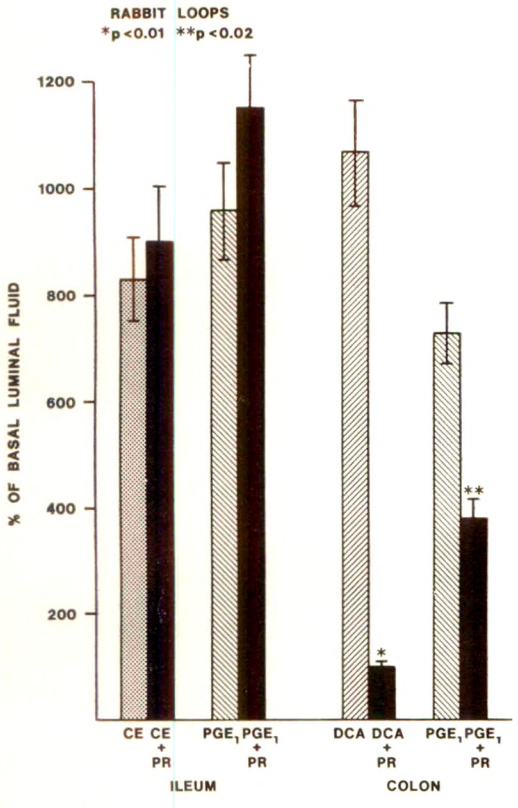


Fig. 4—Effect of PR on CE-, PGE_1- and DCA-stimulated net secretion in the ileum and colon. PR did not affect CE- or PGE_1-stimulated net secretion in the ileum, completely inhibited DCA stimulation of net secretion in the colon but only partially, yet significantly ($P < 0.02$) inhibited PGE_1 stimulation of net secretion in the colon.

Materials:—^3H cAMP (38.4 Ci/mmole), 8-^{14}C-ATP (46.7 mc./mmole) and Aquasol scintillation fluid were obtained from New England Nuclear, Boston, MA. Nonradioactive cAMP and theophylline were obtained from Calbiochem, San Diego, CA. Anion exchange resin (Bio-Rad AG-1-X2, Cl-, 100-200 mesh) was obtained from Bio-Rad Laboratories, Richmond, CA. Snake venom (5′-nucleotidase) and BSA were obtained from Sigma Chemical Co., St. Louis, MO. The sodium salt of DCA (98% pure by gas-liquid chromatography analysis) and reagent grade chemicals were obtained from Matheson Coleman and Bell, Norwood, OH. PR [1-(isopropylamino)-3-(1-naphthyloxyl)2-propanol] hydrochloride (Inderal) was supplied by Ayerst Laboratories, New York, NY. CE, lot A2-2301, was purchased from Schwarz/Mann, Orangeburg, NY. The sodium salt of PGE_1 was supplied by Dr. John Pike of Upjohn Laboratories, Kalamazoo, MI.

Results

CE and PGE_1 in the ileum caused significant ($P < 0.01$) increase in AC activity (Fig. 1) and net secretion (Fig. 2) and DCA and PGE_1 in the colon caused significant ($P < 0.01$) increase in AC (Fig. 1) and net secretion (Fig. 2). PR did not significantly alter basal ileal or colonic AC. (Inhibition of basal secretion cannot be measured in this model.)

PR had no effect on the stimulation of AC or net secretion induced by CE and PGE_1 in the ileum (Figs. 3 and 4). In contrast, in the colon, PR partially inhibited ($P < 0.01$) the stimulation by PGE_1 of AC (Fig. 3) from 265 ± 18% to 166 ± 7% of basal activity and partially inhibited ($P < 0.02$) the stimulation by PGE_1 of net secretion (Fig. 4) from 730 ± 60% to 380 ± 38% of basal. Figures 3 and 4 also show the complete inhibition by PR of DCA stimulation of AC and net secretion in the colon.

PDE was unaffected by PGE_1, CE, or DCA in the colon or ileum with or without PR pretreatment. The average PDE activity was 249 ± 12 pmole/mg. of protein/min.

Comment

We have distinguished colonic AC stimulated by PGE_1 or DCA from small bowel-AC stimulated by PGE_1 or CE. This suggests that the intestinal inhibitory action of PR is site-specific to the colon.

Recently, however, DCA has been shown to stimulate AC and net secretion in the ileum,[17] whereas it had no effect in the jejunum.[1] Accordingly, the effect of PR on DCA-stimulation in the ileum also should be determined. Also, PR blockade of CE-stimulated secretion and dissociation between this secretion and AC in rat intestine has been reported in a recent abstract.[18] Whether the dose, time and means of administration of PR and species differences provide adequate explanation for these conflicting observations remains to be determined.

PR has been shown in this study to significantly but incompletely inhibit the PGE_1-stimulation of AC and net secretion in the colon while having no effect in the small bowel. DCA-stimulated AC and net secretion in the colon, however, was completely inhibited by PR, as previously reported.[9] Thus, at least two different AC's in the colon might be postulated: One stimulated by either DCA or PGE_1 and inhibited by PR; the other stimulated only by PGE_1 and not inhibited by PR. This latter AC could be similar to that stimulated by PGE_1 in the small bowel. CE also stimulates a small bowel-AC that is not inhibited by PR but CE differs from PGE_1 in not stimulating AC in the rabbit colon. Another possibility is that at the doses used, in the colon the AC stimulated by PGE_1 may be more resistant to inhibition by PR than is the AC stimulated by DCA. Alternatively, the ileum may have had a higher level of PGE_1 than the colon because of greater absorption of PGE_1 in the ileum. Finally, dose-response, time-course studies are needed for a more definitive explanation of our findings, even though PGE_1 increased ileal and colonic AC and net secretion by a similar amount (not statistically different percentages.)

PGE_1 has been shown to stimulate AC and secretion in the small intestine of animals[2, 3] and man.[4] The effect of PGE_1 on the cAMP system in the colon, however, is not known. The only reported study indicated no affect of prostaglandins F_{2a} and E_2 on colonic secretion in man.[19] We have shown that PGE_1 is equally potent in the colon and ileum as a stimulant of AC and net secretion in the rabbit. PGE_1 did not affect PDE so that mucosal cAMP content must have increased.

Prostaglandins have been implicated in diarrhea associated with medullary carcinoma of the thyroid, pheochromocytoma and other neural crest tumors[20, 21] and cause diarrhea as a side-effect in its use as an abortifacient[22] and as experimental therapy for peptic ulcer.[23] The results of this study imply that colonic secretion as well as small bowel secretion may play a role in PGE_1-related diarrheas. Furthermore, because PR partially inhibits colonic secretion induced by PGE_1, it warrants evaluation as treatment for diarrhea caused by prostaglandins.

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Watery Diarrhea Syndrome with Elevated Levels of Vasoactive Intestinal Polypeptide Associated with Pancreatitis and Pancreatic Pseudocyst

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A 32-year old patient presented with recurrent pancreatitis, severe watery diarrhea and elevated serum levels of vasoactive intestinal polypeptide. His diarrhea appeared to respond to intramuscular propantheline. Initially he improved but had another attack of pancreatitis while hospitalized. Evaluation by ultrasound revealed the presence of a pseudocyst and endoscopic retrograde pancreatography demonstrated complete occlusion of the main pancreatic duct. Exploratory laparotomy was performed with drainage of a pseudocyst. Analysis of the pseudocyst fluid revealed an elevated amylase, lipase and vasoactive intestinal polypeptide level. It is believed that this patient's severe diarrhea was related to his pancreatitis and pancreatic pseudocyst with elevated levels of vasoactive intestinal polypeptide.

The watery diarrhea syndrome was first described in 1958 by Verner and Morrison in association with pancreatic islet cell adenomas.[1] Since then it has been recognized that this syndrome may occur in diffuse nonbeta pancreatic islet cell hyperplasia, bronchogenic carcinoma, pheochromocytoma, ganglioneuroblastoma and possibly medullary carcinoma of the thyroid.[2-4]

In addition to severe refractory watery diarrhea the syndrome may include hypokalemia, achlorhydria, hyperglycemia, hypercalcemia, hypotension and episodes of flushing.[3, 5] The most life-threatening feature, however, is the severe diarrhea.

We have recently seen a patient with the watery diarrhea syndrome in association with an attack of pancreatitis and pancreatic pseudocyst. His diarrhea appeared to respond to treatment with propantheline bromide (Pro-Banthine®).

Case History

J. B., a 32-year old black male, was admitted to the Martinez Veterans Hospital on 16 September 1976 for the evaluation of nausea, vomiting, abdominal pain, diarrhea and pain in the left leg. The patient had a long history of heavy alcohol consumption and had had several admissions in the past for alcoholic hepatitis. In 1975 he was admitted with pancreatitis and was found to have a pseudocyst which was 3 × 4 × 3 cm. by ultrasonography. There was no history of diarrhea at that time. The pseudocyst resolved with medical management and the patient did well until the present admission. Two weeks prior to this admis-

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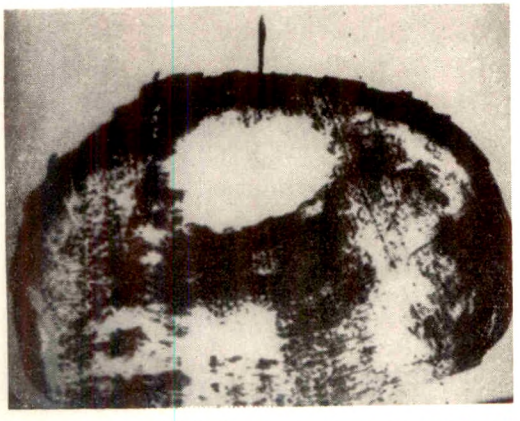


Fig. 1—Large 5 × 8 cm. cystic mass consistent with a pseudocyst visualized by abdominal sonography in the mid abdomen.

sion the patient noted the onset of diarrhea which he could not describe precisely. Approximately one week prior to admission he noted the onset of nausea, abdominal pain and vomiting to the point where he could no longer consume his daily intake of alcohol. Admission history also revealed that the patient had pain in his left calf. The duration of that pain could not be determined.

Physical examination revealed an undernourished black male with clinical signs of dehydration. The liver was palpable 6 cm. below the right costal margin. There were no masses palpable in the abdomen. There was a palpable venous cord in the left calf and edema. The remainder of the physical examination was within normal limits.

Laboratory data on admission revealed a potassium of 1.9 mEq./l.; sodium, 149 mEq./l.; chloride, 114 mEq./l.; CO_2, 19 mEq./l.; BUN, 18 mEq./l.; glucose, 282 mg.%; $mg.^{++}$, 1.1 mg.% and serum amylase, 326 units/100 ml. (normal < 200 units/100 ml.) and a urine amylase of 6.10 DU/min. (normal < 5.4 DU/min.). Chest x-ray was normal, abdominal x-ray revealed a nonspecific gas pattern, a questionable sentinel loop and extensive calcification in the region of the pancreas.

He was treated initially with nasogastric suction, bed rest and intravenous fluids. His diarrhea persisted, however, and he was found to be excreting 5-6 liters of rectal fluid per day. After one week he continued to require large volumes of intravenous fluids and he was begun on propantheline 15 mg. every eight hours in an attempt to decrease his secretory diarrhea. There appeared to be a slight decrease in relation to the dose that was not apparent for several hours before receiving the next dose. The propantheline was then increased to every four hours. At that time the diarrhea ceased. After four days the propantheline was discontinued and the patient's diarrhea did not return. He had one further episode of diarrhea later in his course which was short-lived. During the initial course of diarrhea serum levels of vasoactive intestinal polypeptide were obtained and ranged from 265 pg./ml.-430 pg./ml.

Ultrasound examination (Fig. 1) revealed the presence of a pseudocyst (5 × 8 cm.) in the area of the tail of the pancreas, different from the pseudocyst noted in 1975. Angiography was performed and demonstrated the pseudocyst but other abnormalities suggesting a tumor were not seen. Stool cultures and gram stains were negative. Examination of the stool for ova and parasites was negative. Urine 5-HIAA, urine metanephrines, T3, T4, serum gastrin levels, fecal fat, parathyroid hormone, alpha fetoprotein serum cortisols were all normal. Carcinoembryonic antigen was elevated to 14.9 mg./ml., and serum thyrocalcitonin was elevated to 207 pg./ml. (nl < 100). Thyroid scan, brain scan and electroencephalogram were all normal. During the first week of hospitalization the chest x-ray showed a left upper lobe in-

filtrate felt to be secondary to aspiration which cleared on antibiotic therapy. Upper gastrointestinal endoscopy revealed compression of the stomach by an extrinsic mass and obstruction of the duodenum by extrinsic pressure.

Colonoscopy revealed only nonspecific inflammation on the medial aspect of the ascending colon. Endoscopic retrograde cholangiopancreatography revealed complete obstruction of the pancreatic duct and cholelithiasis.

Ten weeks after admission the patient experienced abdominal pain and the serum amylase was elevated to 1,170 units/100 ml. Serum VIP was 1,150 pg./ml. but the patient did not develop diarrhea. Exploratory laparotomy and drainage of the pseudocyst with cholecystectomy was performed 11 weeks after admission. Analysis of the pseudocyst fluid revealed an amylase of 15,000 units/100 ml., a lipase of 10,700 I.U. and a VIP level of 6,400 pg./ml. Postoperatively the patient developed a subdiaphragmatic abcess which was drained. Subsequently the patient did well and was discharged. He continues to do well with no further diarrhea seven months from his initial admission.

Comment

Vasoactive intestinal peptide (VIP) was isolated from the upper small intestine of the pig in 1970.[6] Since then there have been numerous reports documenting elevated levels of VIP in patients with the watery diarrhea syndrome.[3, 7, 8] Vasoactive intestinal polypeptide stimulates intestinal secretion of water and electrolytes[9] probably by stimulating adenylate cyclase and production of cyclic 3′, 5′-adenosine monophosphate, similar to the mechanism of the secretory diarrhea observed with cholera enterotoxin and certain prostaglandins.[10]

Recommended therapy for the syndrome has been the surgical removal of the adenomas. Because of the difficulty in finding the adenomas and because sometimes there is diffuse hyperplasia of the islets, a total pancreatectomy is often necessary.[11] Metastases, however, already have occurred in 37% of cases by the time of diagnosis.[2] In addition carcinomas other than pancreatic have been associated with peptide secretion and watery diarrhea.[2-4] When surgical removal is not possible or successful, therapy with corticosteroid has led to reduction in the diarrhea in some cases.[2]

The mechanism of action of propantheline in reducing the diarrhea in this patient is speculative. Propantheline is widely known to decrease gastric secretion but it also decreases pancreatic secretion.[12] It has also been shown to affect small intestinal secretion.[13] In addition to its effects on gastrointestinal secretion, propantheline also is known to affect gastrointestinal motility. There is a decrease in intestinal tone with peristaltic contractions showing decreased amptitude and frequency.[14] Possibly the decrease in transit time allows for more effective absorption.

The possibility of a complex neurohormonal interaction, however, needs to be considered. It has been postulated that there are interacting receptor sites for neural and local humoral transmitters.[15] Pharmacochemical tone is set by these sites and permits optimal performance of hormonal sites.[15] In gastric secretion, elimination of one site by vagotomy[16] or an H2 receptor antagonist[17] blocks the response to other forms of stimulation such as gastrin, histamine, and feeding. This mechanism most likely is involved in other types of neurohormonal interaction. Perhaps the medical vagotomy, induced by propantheline, inhibits the action of VIP on hormonal receptor sites. It is doubtful that pro-

pantheline can reduce circulating VIP levels since recent work has shown that atropine does not inhibit the release of VIP caused by vagal stimulation.[18]

The response of the patient described above to propantheline suggests that this agent may be useful in cases where surgical cure is not possible and also in the preoperative management of the watery diarrhea syndrome.

The extensive evaluation carried out on the patient ruled out most of the disorders known to occur in association with the watery diarrhea syndrome such as bronchogenic carcinoma, pheochromocytoma, neural tumors and medullary carcinoma of the thyroid.[2-4] Direct visualization, angiography. endoscopic retrograde pancreatography and ultrasound examination of the pancreas did not detect carcinoma or adenoma of the pancreas. But, since pancreatic tissue was not obtained, the possibility of a small adenoma or the presence of benign idiopathic islet cell hyperplasia remains.

How pancreatitis or pancreatic pseudocyst can cause elevated levels of VIP remains speculative. Normal pancreatic tissue produces vasoactive intestinal polypeptide but serum levels are normally less than 200 pg./ml.[5] It has been postulated that, since VIP is present in high concentration in normal intestine, inflammation of the bowel wall may cause secretion of VIP.[3] No cases, however, have yet been reported. It remains possible that the inflammation associated with this patient's pancreatitis caused hyperplasia of VIP secreting cells with secretion of the peptide and elevated blood levels which resulted in profuse watery diarrhea.

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Superior Mesenteric Artery Compression Syndrome

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An attempt was made to search the medical records of the University Hospital and five affiliated hospitals at Rochester, NY for the last 10 years. Seventeen patients with superior mesenteric artery compression syndrome were found. The prevalence of this disease in a chronic-care hospital (0.965/1,000 admissions) is significantly higher than that in acute general hospitals (0.0108-0.0520/1,000 admissions) by Chi square statistic ($P < 0.001$). This syndrome should be suspected in patients with chronic wasting diseases who are bedridden and have lost weight after which they develop frequent vomiting or aspirations. On reviewing 146 cases from the literature after 1963, duodenojejunostomy was considered to be the best procedure for severe cases. The same good results were not achieved after gastrojejunostomy and lysis of the ligament of Treitz. Gastrojejunostomy provided adequate decompression of the stomach but was inadequate for releasing duodenal obstruction. Some patients after division of the ligament of Treitz had difficulty in downward displacement of the duodenum and the symptoms of obstruction persisted necessitating duodenojejunostomy.

This paper demonstrates that in two patients gastrojejunostomy failed to relieve the obstruction. One of them had to be reoperated on and a duodenojejunostomy was performed with relief of obstructive symptoms.

The superior mesenteric artery compression syndrome is an unusual form of high intestinal obstruction. It was first described by Rokitansky[1] in 1842. Subsequently, Wilkie[2] reported the first comprehensive series of 75 cases in 1927. Since then, a number of reports[3-5] reviewed this syndrome and discussed its treatment. In spite of all these reports, the best surgical procedure for the relief of obstruction due to superior mesenteric artery compression is still not settled.

The purpose of this paper is to emphasize the higher incidence of this syndrome in a chronic patient care hospital and to discuss the appropriate management of this entity.

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Materials and Methods

During the past year, two patients were seen with superior mesenteric artery compression syndrome at Monroe Community Hospital. These cases stimulated us to investigate the incidence in the University and its other five affiliated hospitals, in Rochester, NY. A computer file system search was made in each hospital. The years and results of this survey are summarized in Table I. Although our original plan was to do a ten-year survey, the years surveyed are different in the various hospitals because the filing systems were established

TABLE I

PREVALENCE OF SUPERIOR MESENTERIC ARTERY COMPRESSION SYNDROME IN ROCHESTER AFFILIATED HOSPITALS

Hospital	Years of survey	Total admissions	No. of patients	Prevalence (/1,000)
Monroe Community	1974-1976 (Sept.)	3,108	3	0.965
Strong Memorial	1965-1975	188,462	5 (1)*	0.0265
Rochester General	1965-1975	183,853	2 (0)	0.0108
Genesee	1969-1975	96,029	5 (1)	0.0520
Highland	1970-1975	55,788	1 (0)	0.0179
St. Mary's	1970-1975	53,641	1 (1)	0.0186

* The number within the parentheses indicates the number of patients who were found after 1974.

at different times. Total admissions include all patients other than newborn and obstetric cases. The case search was made under the code number of superior mesenteric artery compression syndrome. All charts with this diagnosis were reviewed for clinical history, upper gastrointestinal series, medical and surgical treatment. Only those cases which were established by upper gastrointestinal series were included in this survey. These cases are summarized in Table II.

CASE REPORTS

Case 1:—P. H., a 32-year old Caucasian female, developed rapidly progressive multiple sclerosis in 1971. She progressed to spastic quadraplegia in 1973 and had been bedridden since then. In March, 1976 she developed abdominal distention and intermittent projectile vomiting. There was a history of a progressive weight loss prior to the the development of obstructive symptoms. She lost 4.5 kg. in one month prior to the time we were asked to see the patient. The abdominal x-rays revealed gastric dilatation. Gastroscopy did not reveal any mucosal or obstructive lesion. An upper gastrointestinal barium study showed a dilated duodenum with an abrupt obstruction at the third portion of the duodenum (Fig. 1). She was treated with nasogastric tube decompression and I.V. fluids but the obstruction persisted. A laparotomy was done on 14 April 1976 and the duodenum was found to be markedly dilated up to the point of the superior mesenteric artery. The case was discussed with the surgeons and a plan for a duodenojejunostomy (proximal to the superior mesenteric artery) was made. For some unknown reason, the decided plan was not carried out and a simple gastrojejunostomy was performed. Postoperatively, she continued to have large amounts of NG drainage and a distended abdomen. The Hypaque gastrointestinal study again showed the dilated duodenum with an obstruction at the third portion of the duodenum (Fig. 2). On 25 April she underwent duodenojejunostomy and closure of the gastrojejunostomy. Her symptoms disappeared after the second operation. Follow-up upper gastrointestinal x-ray demonstrated no duodenal stasis (Fig. 3). The patient has remained asymptomatic since then.

Case 2:—G. W., a 68-year old Caucasian male developed intermittent abdominal pain, nausea and vomiting. A flat film of the abdomen suggested duodenal obstruc-

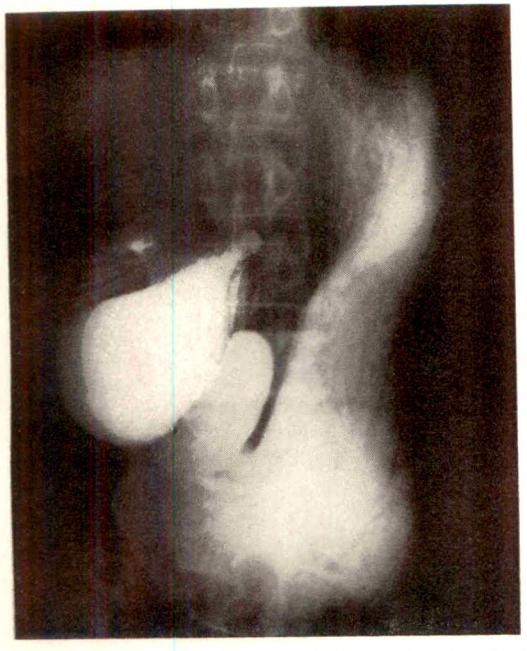


Fig. 1—Preoperative upper gastrointestinal series in Case 1 demonstrating the straight line, or sharp cut off, obstruction to the passage of barium in the third portion of the duodenum and marked dilatation of the proximal duodenum and stomach.

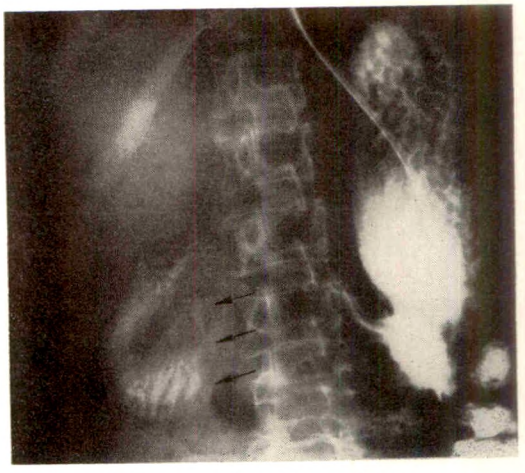


Fig. 2—After gastrojejunostomy, Hypaque upper gastrointestinal study showing persisting distal duodenal obstruction (arrows) and dilatation of duodenum, although gastrojejunostomy is functioning well.

tion. He underwent a laparotomy on 14 January 1972. No intestinal obstruction or other abdominal pathology was found. After laparotomy, he continued to have the same symptoms. A cholecystogram and a gastroscopy were done which revealed no abnormality. An upper gastrointestinal barium study on 8 March showed a dilated stomach and duodenum and a straight line cut off at the third portion of the duodenum. He was explored again on 16 March and a gastrojejunostomy was done. An adenocarcinoma in the pancreatic body was also detected at surgery without any metastases to the intestine and it was not considered to be causing any obstruction. Postoperatively, his nausea and vomiting persisted. The patient died in six months from his pancreatic cancer.

Case 1 clearly illustrates that gastrojejunostomy relieved the gastric obstruction but was not adequate for duodenal obstruction. The patient's symptoms persisted which disappeared after duodenojejunostomy. In Case 2, the patient's symptoms persisted after gastrojejunostomy. Although no follow-up barium meal upper gastrointestinal study was taken, we feel the nausea and vomiting were due to duodenal obstruction. The possibility of pancreatic cancer causing any obstruction was ruled out at surgery.

Case 3:—W. D., a 15-year old black boy, was involved in an automobile accident in 1974 and suffered severe brain damage requiring gastrostomy tube feeding. He has been bedridden for more than two years and developed contracture of his extremities. In late August, 1976, corrective surgery was done for the contractures of his wrist. He developed repetitive episodes of vomiting and aspiration pneumonia after surgery. An upper gastrointestinal x-ray showed a straight line cut off at the third portion of the duodenum and dilatation of the proximal duodenum. He was treated conservatively without success. Duodenojejunostomy was done in September, 1976.

TABLE II

SUMMARY OF CASES

Patient	Age	Sex	Wt. (kg.) Ht. (cm.)	Wt. loss prior to surgery	Medical Rx prior to surgery	Peptic ulcer	Emotional problem	Other associated problems	Treatment surgical/ medical	Outcome
1. P.H.	32	F	41/100	+	+	–	–	Multiple sclerosis	GJ DJ	S/S persisted after GJ, No S/S for 9 mo. after DJ
2. G.W.	68	M	51.75/NR	+	NR	–	–	CA of pancreas	GJ	S/S persisted
3. W.D.	16	M	49/180	+	+	–	–	Brain injury	DJ	No S/S for 2 mo.
4. J.J.	60	M	43.2/165	+	+	–	–	Scleroderma	DJ	Symptoms relieved but died of underlying disease
5. K.R.	27	F	54/163	+	+	–	–	–	DJ	Discharge in 10 days, no follow-up
6. M.S.	32	F	45.5/155	+	+	+	+	–	DJ	Improved initially, recurrent S/S in 1 yr. responded to Valium, normal UGI
7. M.E.S.	29	F	57.6/166	+	+	+	–	–	DJ	Discharged in 8 days, good results, no follow-up
8. M.W.	28	F	47.7/155	+	+	–	+	–	DJ	No recurrence in 2 yr. follow-up
9. B.A.	17	F	45.9/158	NR	+	–	–	–	LLT	Discharged in 12 days without S/S No follow-up

S/S = signs and symptoms
GJ = gastrojejunostomy
DJ = duodenojejunostomy
LLT = lysis of the ligament of Trietz
NR = not recorded

TABLE II *(continued)*

SUMMARY OF CASES

Patient	Age	Sex	Wt. (kg.) Ht. (cm.)	Wt. loss prior to surgery	Medical Rx prior to surgery	Peptic ulcer	Emotional problem	Other associated problems	Treatment surgical/ medical	Outcome
10. R.M.	10	M	28.8/NR	NR	NR	–	+	–	LLT	Discharged in 1 wk., no follow-up
11. M.M.	16	M	49.5/178	NR	NR	–	+	–	LLT	Recurrent S/S in 2 yr. due to adhesion
12. M.F.	24	F	41/155	NR	+	–	+	–	LLT and DJ	GI symptoms in 8 mo., follow-up in psychiatric clinic
13. M.A.	71	M	47.7/166	+	+	–	–	COPD, ASHD, previous abdominal surgery for colon CA	Med.	Relieved in 6 days, no symptoms for 2 yr.
14. C.R.	19	F	50/NR	NR	+	–	–	Pregnancy	Med.	Relieved in one wk., no follow-up
15. J.T.	26	F	52.7/173	+	+	–	–	Open heart surgery for congenital aortic insufficiency and VSD	Med.	Relieved in 2 days, no follow-up
16. W.R.	13	M	41/155	NR	+	–	–	Scoliosis	Med.	Relieved in 2 wk. no follow-up
17. P.W.	22	F	47.3/NR	NR	+	+	–	1st trimester of pregnancy	Med.	Relieved in 1 wk., no follow-up

S/S = signs and symptoms
GJ = gastrojejunostomy
DJ = duodenojejunostomy
LLT = lysis of the ligament of Trietz
NR = not recorded

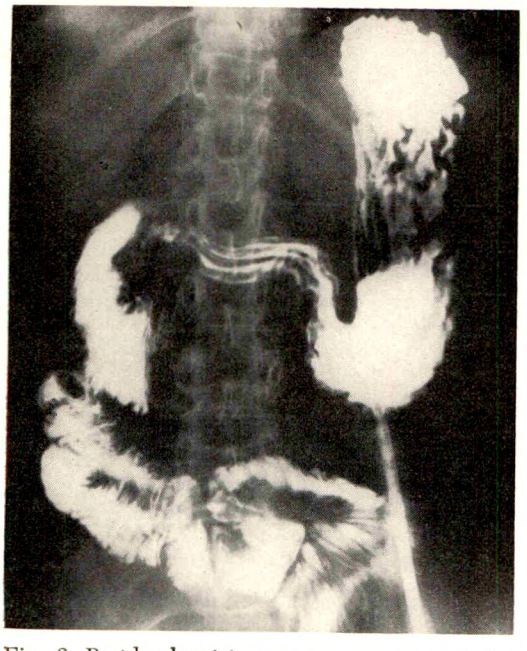


Fig. 3—Postduodenojejunostomy upper gastrointestinal barium study showing a well functioning duodenojejunostomy. No duodenal dilatation, retention or obstruction.

The obstruction was released. He tolerated the gastrostomy tube feeding well and gained 4.5 kg. in weight during one month. The follow-up upper gastrointestinal barium x-ray showed no duodenal obstruction.

Table II summarizes the clinical pictures and outcomes of treatment of 17 patients with this syndrome. Cases 4 through 8 had medical histories of upper gastrointestinal obstruction similar to the three cases described above. All had duodenojejunostomy with good results as in Case 3. Cases 9 through 11 had lysis of the ligament of Treitz and downward displacement of the duodenum. Case 12 had duodenojejunostomy and division of the ligament of Treitz at the same time. Cases 13 through 17 were treated conservatively.

Comment

Superior mesenteric artery compression syndrome is a rare disease, but the true incidence is not known. Goin and Wilk[6] reviewed a series of 2,080 upper gastrointestinal x-ray examinations and found seven clinically symptomatic cases of vascular compression of the duodenum (prevalence 0.3%). Nugent, et al[7] found only five cases in 38,000 upper gastrointestinal x-rays (0.013%). The present study revealed the prevalence of this disease at one university hospital and its affiliated general hospitals to be 0.0108-0.0520/1,000 admissions (Table I). The prevalence of this disease at one general hospital (Genesee) was slightly higher than that in the other four hospitals and the university hospital. It should be mentioned, however, that Genesee Hospital has a large gastroenterological center which attracts a large proportion of the patients with gastrointestinal problems. The prevalence of this disease at Monroe Community Hospital was significantly higher as compared to the pooled sample from the other five hospitals using Chi square statistic ($P < 0.001$). A good medical record filing system was not established until 1974 at Monroe Community Hospital and so we were able to survey only 3,108 cases. In our opinion the higher prevalence in this hospital was not due to any bias because of small sample size or the difference of the years surveyed. Even if one had compared the number of cases found after 1974 in all the hospitals, the higher incidence in the Monroe Community Hospital was again evident (Table I). The patient population of Monroe Community Hospital is different from other general hospitals. Most of the patients at Community Hospital are chronically ill, bedridden with nutritional problems and weight loss. Although the patient population at Monroe Community Hospital is older than that in the other hospitals, two out of three patients with this syndrome are fairly young (ages below 32). Therefore, age alone could not be the determining factor for the higher incidence of this disease observed.

TABLE III

RESULTS OF VARIOUS TREATMENTS—SUMMARY OF THE LITERATURE

Author	No. of cases	Conservative	GJ	DJ	LLT	LLT* and DJ	Other
Appel, et al[5]	3	1		2(1)†			
Akin, et al[4]	10				7(1)	2(1)	1
Paul, et al[23]	5			5			
Anderson, et al[17]	32	16(7)	5(3)	4(1)			7(5)
Puranik, et al[24]	7	3		2	1(1)		1
Wayne, et al[11]	7	2		1	4		
Guthrie[25]	2						1
Evarts, et al[26]	13	6(1)	1	5	1		
Wayne, et al[13]	5	4		1			
Mindell, et al[22]	3	2		1(1)			
Berk, et al[27]	4	4					
Wallace, et al[28]	3			3			
Mansberger, et al[9]	12	2		7	1	2	
Nelson, et al[29]	1			1			
Hearn[30]	6	1		4	1		
Nugent, et al[7]	5		2	2(1)			1
Kelly, et al[31]	4			3	1		
Reese, et al[32]	2				2		
Cox, et al[15]	1				1		
Schwartz, et al[33]	1				1(1)		
McKinnon, et al[34]	8		1	7			
Hyde, et al[12]	12	5	1(1)	2	4		
Totals	146	46(8)	11(4)	50(4)	24(3)	4(1)	11(5)

* Failure to free the duodenum after lysis of the ligament of Treitz and duodenojejunostomy performed on the same operation.

† The number in parenthesis indicates poor result of treatment and complications from surgery.

The etiology of the superior mesenteric artery compression syndrome is not well known. The mechanism of duodenal obstruction has been postulated to be the narrowing of the normal angle between the aorta and the superior mesenteric artery.[4, 8-10] The duodenum is sandwiched between the aorta and superior mesenteric artery. A variety of factors has been reported to enhance the narrowing of this angle, i.e. weight loss,[11, 12] prolonged bed rest,[13] asthenic body build,[11, 14] increased lordosis,[8] duodenal ulcer[15-17] and loss of muscle tone of the abdominal wall leading

to visceroptosis.[3, 8] Table II reveals that most of the patients were of asthenic body build and 10 of them had documented weight loss preceding the development of this syndrome.

Considering the above etiological factors of the superior mesenteric artery compression syndrome, some patients should benefit from conservative treatment such as nasogastric tube decompression, improving nutrition, intermittent ambulation, appropriate position of the patient (i.e. right and left lateral decubitus, prone and knee-chest position) and physical exercises to correct accentuated lumbar lordosis and lax abdominal musculature. In our series, five patients (Cases 13-17) responded well to this conservative medical management with relief of symptoms after two to 12 days. Twelve patients, however, required surgery.

In 1963, Barner and Sherman[3] reviewed 277 published cases with superior mesenteric artery compression syndrome. Forty-four of these patients were considered fit to be treated medically and only 22 (50%) had good results. After 1963, 146 cases were reported in the English literature (Table III) out of which 46 patients received conservative therapy. Only eight patients failed to respond to conservative treatment, however, many of the patients who were treated surgically had been tried on medical treatment previously. Since a high population of the patients with superior mesenteric artery compression syndrome have psychosomatic problems[18] and peptic ulcer symptoms,[17] it is even more difficult to assess the results of conservative therapy. The stage of the disease is also a very important factor in determining the result of medical treatment. In the late stage of the disease, the patient usually is unable to eat and has profound weight loss which causes more loss of fat from the retroperitoneum region and omentum leading to progressive narrowing of the aortomesenteric angle. The distended duodenum may become atonic. The atony of the duodenum may not disappear immediately after surgery and may persist for some time.[11, 19]

From our series and other reports in the literature, it is clear that many of the patients with superior mesenteric artery compression syndrome may not respond to conservative medical treatment and may require surgical intervention. The three surgical procedures most commonly used are duodenojejunostomy, lysis of the ligament of Treitz and gastrojejunostomy. Considering the anatomy, gastrojejunostomy should not work since the duodenal obstruction cannot be relieved and the biliary and pancreatic secretion will still distend the duodenum and cause symptoms. In addition, marginal ulcer and blind loop syndrome may happen after gastrojejunostomy. The drawbacks of gastrojejunostomy had been amply cited by Wilkie[20] and others[8, 12] but the procedure has still been used because of its simplicity. Barner and Sherman[3] showed 64% of the patients obtained relief after this operation. Since 1963, 11 more patients with superior mesenteric artery compression syndrome were operated with gastrojejunostomy. The results of gastrojejunostomy were inferior to duodenojejunostomy from most of the series[3, 12, 17] and from our own experience. Gastrojejunostomy relieves the stomach pressure but not the duodenal stasis which may continue to cause symptoms. It is well illustrated in our indexed Cases 1 and 2. Although the surgeons were amply warned against performing gastrojejunostomy alone, they still performed the surgery hoping that it might work in certain cases reported in the literature.[3, 7, 17] The patient (Case 1) was observed for many weeks after the gastrojejunostomy but he remained symptomatic and a duodenojejunostomy was the only alternative.

In 1958, Strong[10] first advocated plastic division of the ligament of Treitz and downward displacement of the duodenum for treatment of the superior mesenteric artery syndrome. He claimed that this procedure was simpler, safer and more physiologic. Wayne and Burrington[11, 21] had succeeded in many of their patients with this procedure. From their experience, this procedure only takes 45 minutes. Because the bowel is not opened, the patient recovers earlier and all of their patients can begin a normal diet in three to five days. Theoretically, it seems the best operative procedure for patients with superior mesenteric artery compression syndrome. Not all of the patients, however, can have their duodenum displaced downward after lysis of the ligament of Treitz because of the interference of short vessels from the inferior pancreaticoduodenal artery to the duodenum.[9] One patient in our series (Case 12), two cases reported by Akin[4] and two cases reported by Mansberger[9] had this difficulty of downward displacement of the duodenum.

Duodenojejunostomy was used more frequently for treatment of superior mesenteric artery compression syndrome. In 277 cases reviewed by Barner and Sherman[3] 161 cases were treated by duodenojejunostomy in which 79% had good results. Our review of cases after 1963 (Table III) revealed that out of 50 cases in which duodenojejunostomy was done, only four had poor results and only one case reported by Nugent[7] could be labeled as a complete failure of this procedure. The problems of the other three patients were not due to the failure to release obstruction of the superior mesenteric artery syndrome but stomal obstruction,[22] efferent loop syndrome[5] and symptoms from prepyloric gastric ulcer.[17] Statistically, the results of duodenojejunostomy are significantly better than the other two procedures by Chi square statistics ($P < 0.01$). All the seven patients except for one (Case 6) in the present series with duodenojejunostomy had good results. Even in Case 6 the persistent symptoms were probably due to psychogenic causes because no obstruction was found in the postoperative upper gastrointestinal barium study. In conclusion, if the patient with superior mesenteric artery compression syndrome does not respond to conservative medical management, surgical intervention is indicated and duodenojejunostomy probably is the procedure of choice.

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The Parotid and the Pancreas*

III. Correlation of Parotid Gland and Pancreatic Secretion After Radiation-induced Chronic Pancreatitis

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Parallel studies in parotid and pancreatic function and histology were carried out in Thomas fistula dogs with irradiation-induced chronic pancreatitis. After completion of base line studies of parotid and pancreatic secretion, four dogs were subjected to 2,400 rads tumor dose over two weeks (with a nominal single dose of 1,175 rets); two additional dogs served as control. Sequential studies were performed on pancreatic secretion in response to secretin and on parotid secretion in response to urecholine. After a short-lived period of hypersecretion. there was a progressive reduction in pancreatic secretory rate, bicarbonate and enzyme outputs ($> 90\%$ after three months). Parotid secretion increased over this period but subsequently decreased, so that at eight months there was a marked reduction both in pancreatic and parotid function. Whereas pancreatic histology showed diffuse interstitial fibrosis and reduction of acinar tissue, no histologic changes were noted in the parotid glands. Although the mechanisms are unclear, alterations in parotid secretion may be of value in the diagnosis of chronic pancreatitis, in the evaluation of its severity, and may yield information on the duration of the disease.

Examination of parotid saliva has been claimed to be a useful diagnostic aid in the clinical diagnosis of pancreatic disorders. Reduction in volume, bicarbonate concentration and amylase content of saliva has been noted in patients with pancreatic diseases.[1-3] Experimentally produced acute pancreatitis, has resulted in hypofunction and atrophy of the parotid gland.[4] In the present study we investigated the relationship between parotid gland and pancreatic function in irradiation-induced chronic pancreatitis.

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TABLE I

PANCREATIC SECRETION IN FOUR DOGS SUBJECTED TO IRRADIATION

	Volume ml./15 min.	HCO_3 concentration mEq./l.	HCO_3 output mEq./15 min.	Protein (enzyme) concentration mg./ml.	Protein (enzyme) output mg./15 min.
Before irradiation	26.8 ± 2.3	128.8 ± 2.85	3.45 ± 0.01	4.1 ± 1.8	110.53 ± 0.8
2 wk. after irradiation	32.6 ± 3.8	127.3 ± 9.02	4.15 ± 0.02	2.8 ± 0.8	92.96 ± 0.15
4 wk. after irradiation	27.8 ± 2.2	118.0 ± 7.31	3.28 ± 0.02	3.0 ± 0.2	84.57 ± 0.25
6 wk. after irradiation	20.9 ± 2.7	118.0 ± 3.38	2.49 ± 0.04	2.7 ± 0.4	57.64 ± 0.80
8 wk. after irradiation	9.4 ± 3.2	97.5 ± 12.24*	0.91 ± 0.01*	2.7 ± 0.4*	25.85 ± 1.12*
3 mo. after irradiation	9.0 ± 4.8*	87.8 ± 19.13*	0.79 ± 0.03*	2.8 ± 0.8*	25.55 ± 1.25*
4 mo. after irradiation	1.9 ± 0.7†	92.4 ± 6.5 *	0.18 ± 0.04†	‡	‡
5 mo. after irradiation	1.1 ± 0.5†	‡	‡	‡	‡

* $P < 0.05$
† $P < 0.01$
‡ Volumes too low to allow accurate measurement

METHODS

Six mongrel dogs of both sexes weighing 18-24 kg. were prepared with Thomas cannulae[5] in the duodenum opposite the major pancreatic duct; the accessory duct was ligated and divided. Silver clips, placed in the mesentery of the pancreas around the periphery of the gland, permitted accurate localization, so that irradiation would include but be limited to the entire gland. Biopsy of the pancreas for histological examination was taken at this time in all the animals. Secretory studies on the parotid gland and the pancreas were commenced three weeks later.

After completion of the control studies the animals were divided into two groups: Group I (four dogs). The pancreas was localized under radiologic control and ^{60}Co radiotherapy delivered with a Theratron 80. A tumor dose of 400 rads was delivered on alternate days in six sessions, to a total of 2,400 rads (the equivalent biologic effect of 4,000 rads tumor dose over six weeks in humans). Each dose was delivered with the dog under anesthesia on alternate days to avoid the undesirable effects of daily anesthesia. To compensate for the increased biological effect, the ret equivalent of 4,000 rads in six weeks (treatment five days/week) was decreased 15%. Group II (two dogs). These were used as control. Secretory studies were performed at similar time schedules to Group I.

Each experiment was carried out with the animal in the conscious state, standing calmly in a harness and deprived of food but not water for at least 18 hours. Animals

TABLE II

PANCREATIC SECRETION IN TWO CONTROL DOGS

	Volume ml./15 min.	HCO_3 concentration mEq./l.	Protein (enzyme) concentration mg./ml.
Control	24.6 ± 1.8	131.1 ± 3.8	4.6 ± 1.3
After 2 wk.	25.9 ± 1.6	134.1 ± 4.1	4.1 ± 1.6
After 1 mo.	24.4 ± 2.3	129.6 ± 2.9	4.8 ± 1.1
After 2 mo.	26.7 ± 2.3	134.6 ± 3.4	3.7 ± 1.3
After 4 mo.	24.2 ± 2.2	133.5 ± 3.7	3.9 ± 1.6
After 8 mo.	25.6 ± 1.9	132.4 ± 3.2	4.7 ± 1.9

were studied no more than two to three times a week and never on consecutive days. A continuous intravenous infusion of 0.15 M sodium chloride was maintained throughout each experiment to allow for fluid losses. The main pancreatic duct was cannulated under direct vision through the Thomas cannula. Pancreatic secretion was collected at ten-minute intervals in the resting state and five-minute intervals in the stimulated experiments. The secretory stimulants used were pure natural secretin. (Gastrointestinal Hormone Research Unit, Stockholm, Sweden) 1 U./kg. and 4 U./kg. Experiments were also conducted with continuous intravenous infusions of secretin 0.03 U./kg./min. and cholecystokinin-pancreozymin (Cecekin, Gastrointestinal Hormone Research Unit, Stockholm, Sweden) 0.05 U./kg./min. In all experiments both hormones were from the same batches; the order of injections or infusions was randomized. At least three control studies of each stimulus were obtained prior to the commencement of irradiation. Secretory studies were repeated after each dose of radiation. After completion of the course of radiation, secretory studies were carried out at weekly intervals.

Parotid secretion was collected with the animals in the anesthetized state (Phenobarbital 0.35 mg./kg. I.V.I.). With the animal lying on its left side a Lashley saliva cup was placed over the papilla of the right parotid duct. The cup was maintained in position by gentle suction. Basal secretion was collected in five-minute periods for 30 minutes. Urecholine 0.25 mg./kg. was administered subcutaneously and saliva was again collected in five-minute periods for 30 minutes.

At least three tests of pancreatic and salivary secretion were performed at each stage. Pancreatic and parotid secretion were always studied on separate days. Individual samples were collected under oil and analyzed for volume, bicarbonate and chloride concentrations. Protein (enzyme) concentrations of pancreatic juice and amylase concentration of saliva were also measured. Bicarbonate and chloride concentration were measured with a Technicon Autoanalyzer. Protein concentration was measured by the method of Preshaw, et al[6] and amylase concentration by a modified Somogyi method.

Open biopsies of the pancreas and parotid glands were taken in both control dogs and in two of the irradiated dogs six to eight months after completion of the irradiation.

TABLE III

PAROTID SECRETION IN FOUR DOGS SUBJECTED TO IRRADIATION

	Volume ml./min.	HCO_3 concentration mEq./l.	HCO_3 output mEq./min.	Amylase concentration U./ml.	Amylase output U./min.
Before irradiation	0.83 ± 0.04	40.6 ± 3.3	0.03 ± 0.01	0.85 ± 0.1	0.73 ± 0.2
6 wk. after irradiation	0.99 ± 0.15	43.7 ± 3.7	0.04 ± 0.01	0.85 ± 0.26	0.84 ± 0.1
8 wk. after irradiation	1.09 ± 0.20	48.9 ± 4.7	0.05 ± 0.02	0.81 ± 0.16	0.88 ± 0.2
3 mo. after irradiation	1.41 ± 0.15*	47.4 ± 2.5	0.06 ± 0.02	0.37 ± 0.9*	0.52 ± 0.01
4 mo. after irradiation	1.17 ± 0.09*	42.9 ± 2.5	0.05 ± 0.01	0.44 ± 0.08	0.51 ± 0.1†
8 mo. after irradiation	0.24 ± 0.06‡	32.2 2.2‡	0.02 ± 0.0‡	0.10 ± 0.0‡	0.02 ± 0.0‡

* $P < 0.010$
† $P < 0.025$
‡ $P < 0.0010$

RESULTS

Pancreatic secretion in response to secretin was 26.8 ml./15 min. in the control period (Table I). Bicarbonate concentration was 128.8 mEq./l. and protein (enzyme) concentration 4.1 mg./ml. Two weeks after starting the irradiation (at about the time of its completion) there was an increase in the rate of secretion to 32.6 ml./15 min. but this returned to control levels two weeks later. Thereafter, a progressive reduction in flow rates occurred. Two and three months later, volume was only 33% of control values whereas at four months it was 8% and at five months, 5%. Narrowing of the orifice of the pancreatic duct occurred (due to fibrosis), so that it became impossible to cannulate the pancreatic duct after five months.

Bicarbonate concentration and output did not change significantly in the early phase but showed a progressive reduction in concentration and output as the rate of secretion fell off. Enzyme concentration and output, on the other hand, were reduced at an early stage.

Concurrent studies in two nonirradiated dogs (Table II) showed no significant alteration in volume, bicarbonate or enzyme concentrations over the same period.

A somewhat different pattern was noted with parotid secretion. Control values were: volume, 0.83 ml./min.; bicarbonate concentration, 40.6 mEq./l. and amylase concentration, 0.85 U./ml. There was an initial progressive increase in secretion (Table III) so that at two months there was a 31% increase and at three months a 70% increase. A biphasic pattern now occurred, with a gradual decline in secretion. Eight months after irradiation there was a 75% reduction in secretory rate. Bicarbonate concentration and output were affected only after eight months. Amylase concentration and output were already decreased

TABLE IV

PAROTID SECRETION IN TWO CONTROL DOGS

	Volume ml./min.	HCO_3 concentration mEq./l.	Amylase concentration U./ml.
Control	0.98 ± 0.12	44.2 ± 4.1	0.93 ± 0.15
After 1 mo.	0.91 ± 0.11	41.6 ± 3.9	0.86 ± 0.11
After 2 mo.	0.89 ± 0.14	43.6 ± 3.7	0.90 ± 0.13
After 4 mo.	0.96 ± 0.11	44.1 ± 4.3	0.85 ± 0.11
After 8 mo.	0.88 ± 0.13	41.3 ± 3.8	0.92 ± 0.14

after three months. The two nonirradiated dogs showed no change in secretion over the same period of time (Table IV).

In contrast to the two control animals, microscopic evidence of diffuse interstitial fibrosis was noted in the pancreas of the irradiated dogs. There was also a marked reduction of acinar tissue. No significant histologic changes were noted in the parotid glands of either group.

COMMENT

The present study confirms our earlier report[7] on exocrine function after irradiation of the canine pancreas. After a short-lived increase in secretory rate, there was a progressive deterioration of all parameters of pancreatic exocrine function. Salivary secretion (Fig. 1) showed a biphasic response, with a period of hypersecretion lasting for three months then going on to deterioration of function. Whereas the pancreas showed histologic features of chronic fibrosing pancreatitis, the alteration in parotid function was unaccompanied by histologic changes.

Because of its accessibility, salivary secretion is often used as a diagnostic aid in aldosteronism, Addison's disease and in forensic medicine for the detection of drugs. Its use as a diagnostic parameter in gastrointestinal disorders has not been fully established. Hypersecretion of gastric acid in duodenal ulcer patients is accompanied by a proportionate increase in salivary secretion.[8] It has been postulated[8] that duodenal ulcer disease is characterized by enlargement of several exocrine glands—the parietal cell system of the stomach, salivary glands and pancreas—while only the enlargement of one gland (the stomach) is related to ulcer symptoms. Salivary gland enlargement has also been observed in patients with alcoholic cirrhosis[9] but may occur in alcoholics in the absence of cirrhosis[10] or in cirrhosis due to other causes.[11]

There are several reports of an association between parotid enlargement and pancreatitis.[12, 13] Alappatt and Ananthachari[14] noted parotid enlargement and increased secretion in patients with chronic relapsing pancreatitis; they found hypertrophy of acinar cells with no apparent change in the duct elements. Kakizaki, et al, on the other hand, in a series of studies,[2, 3, 4] showed hypofunction and atrophic changes in the parotid gland in experimental and clinical pancreatitis.

Kakizaki, et al[3] claim that examination of parotid saliva provides a reliable and rapid test for the diagnosis of pancreatic diseases. They found a reduction in volume, bicarbonate and amylase concentration in patients with chronic pancreatitis

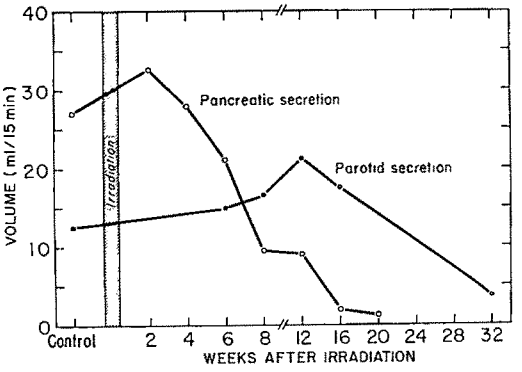


Fig. 1—Alterations in parotid gland and pancreatic secretion in four dogs with radiation-induced chronic pancreatitis.

and other pancreatic disorders. Descos, et al,[1] on the other hand, showed that mixed salivary secretion (volume, bicarbonate and amylase) was decreased under basal conditions in patients with chronic pancreatitis but not when studied under mechanical stimulation. Perhaps there was a reduction in the sensitivity of the oral mucosa to the sucking device in the latter study, since Kakizaki, et al used pilocarpine to stimulate parotid secretion.

Although salivary glands are very sensitive to ionizing radiation whether directly or to tumors in the neighborhood, there are no reports that salivary secretion is affected by radiation to distant sites of the body.

It should be pointed out that our studies only refer to parotid secretion stimulated by urecholine. We did not measure basal secretion, because secretion by parotid, submaxillary or submucosal glands in the dog is not continuous but occurs only in response to exogenous stimulation.[15]

It is not readily apparent why there should be alterations in parotid function in patients and animals with chronic pancreatitis. The digestive glands are able to modify their secretion in response to diet.[16, 17] Parotid hyposecretion may be seen in nutritional deficiency states especially where there is a qualitative and quantitative lack of protein.[12, 18] Perhaps the changes we noted were partially due to malnutrition induced by pancreatic exocrine insufficiency. Our dogs demonstrated biochemical evidence of steatorrhea; the parotid dysfunction might have been related to malabsorption. This clearly requires further study. It would be of interest to determine whether salivary dysfunction could be reversed by the addition of enzyme supplements and whether any dysfunction occurs in nonpancreatic steatorrheas. Wells and Voelkel,[20] however, showed that whereas proteolytic enzymes and pancreatic extract added to food produced salivary hypertrophy, pancreatic extract had no such effect when it was given by intragastric tube. Another factor may have been the weight loss (3-5 kg.) noted in our dogs; there is a well-established relationship between salivary secretion and body weight[2] and between salivary gland size and body weight.[2]

Care must be taken in attempting to transpose our findings to the clinical situation. The chronic pancreatitis was induced by irradiation and not by alcohol, the commonest cause of pancreatitis in this country. Nevertheless, our studies indicate that alterations in parotid secretion may be of value in the diagnosis of chronic pancreatitis, in the evaluation of its severity and may yield information on the duration of the disease.

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Association of Pancreatitis and Variant Ductal Anatomy

Dominant Drainage of the Duct of Santorini

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Four patients with acute relapsing pancreatitis were found to have drainage of the main pancreatic duct through the duct of Santorini and accessory papilla by endoscopic retrograde pancreatography. No other cause of pancreatitis was identified. These cases and the possible significance of this association are discussed.

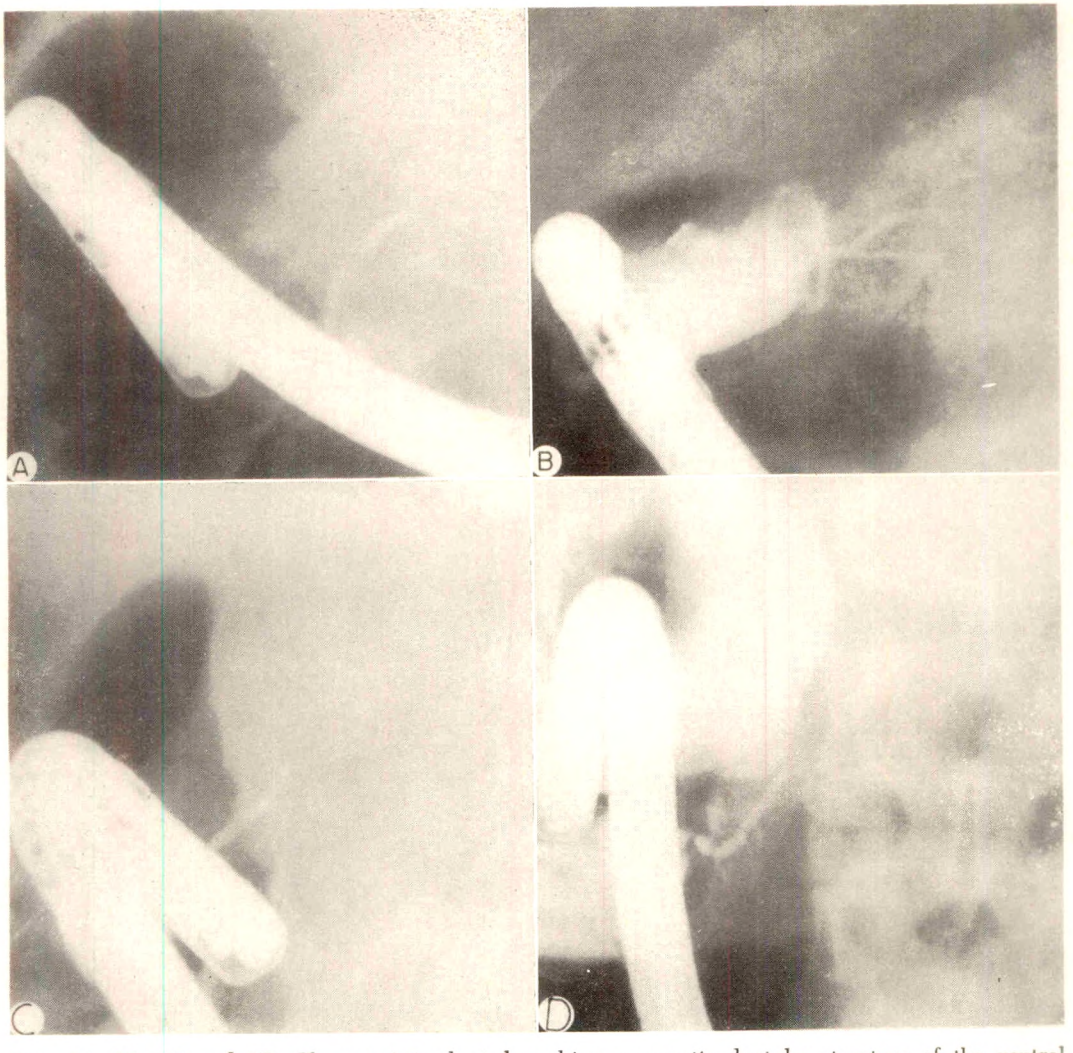
In the majority of patients with pancreatitis, a cause is identified.[1] Chronic alcohol abuse and cholelithiasis are the conditions most commonly responsible. Less often, pancreatitis is related to hyperlipidemia, hypercalcemia, hereditary pancreatitis, trauma and adverse drug reactions. In some parts of the world, *Ascaris* migration and inadequate nutrition cause pancreatitis. Despite careful study, in some patients an apparent cause of pancreatitis cannot be found. In four such patients studied by endoscopic retrograde cholangiopancreatography, a congenital variation was found in the pancreatic duct. The main pancreatic connection to the duodenum was through the accessory papilla and the duct of Santorini. These cases and a discussion of the possible significance of this association are the basis of our report.

None of our patients had family members with a history of pancreatitis. All patients denied significant alcohol consumption. No history was elicited of significant abdominal trauma or use of drugs associated with pancreatitis. All four patients had normal findings on physical examination. In each patient, the findings of oral cholecystography or intravenous cholangiography were normal. Pancreatic calcifications were absent. All patients had normal levels of serum calcium on at least one occasion during a symptom-free interval. Hyperamylasemia was well documented on several occasions in association with episodes of abdominal pain. Each patient had an upper gastrointestinal barium study, and the findings were normal. One patient with diabetes (Case 4) had increased levels of pre-beta lipoproteins and chylomicrons. In the other three patients, lipids were within normal limits.

Case Reports

Case 1:—A 26-year old man was first seen at the Lahey Clinic Foundation in March, 1976 for acute relapsing pancreatitis (Fig. 1A). He had had recurrent abdominal pain since the age of 5. He had been hospitalized on several occasions since 1973 because of left upper quadrant pain radiating to the back associated with hyperamylasemia. Because of recurrent disability, an 85% subtotal pancreatectomy was performed. Pathologic examination showed chronic pancreatitis with dense fibrosis.

From the Department of Gastroenterology, Lahey Clinic Foundation.

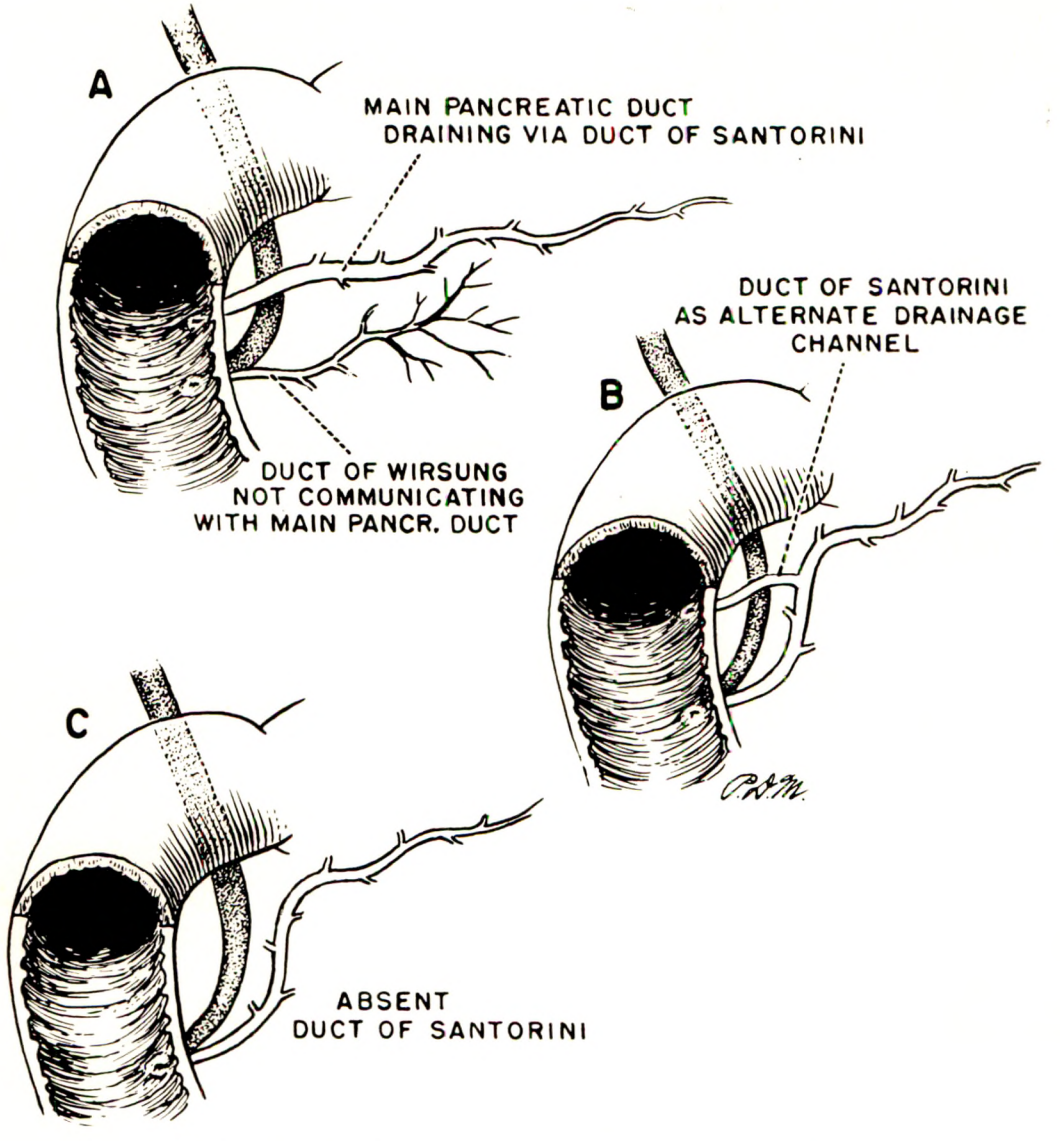


Figs. 1A, 1B, 1C and 1D—Characteristic short, branching pancreatic ductular structure of the ventral pancreatic remnant isolated from the main pancreatic duct.

Case 2:—A 34-year old woman was admitted to the New England Baptist Hospital in January, 1976 for recurrent abdominal pain (Fig. 1B). Six years before admission, she noted the onset of episodes of abdominal discomfort. In September, 1975, hyperlasemia was found when she was hospitalized because of acute abdominal pain, nausea and vomiting.

At operation peripancreatic edema was reported. The surgeon was unable to probe the minor papilla with a needle and its summit was excised. Thereafter, secretin was injected, and copious secretion was observed through the minor papilla with only minimal secretion from the papilla of Vater. Sphincterotomy of the minor and major papilla and cholecystectomy were performed. Calculi were not present. At follow-up examination in May, 1976, the patient reported no further abdominal pain.

Case 3:—A 35-year old woman was seen in June, 1976 for recurrent acute pancreatitis which had been present for the



Figs. 2A, 2B, 2C and 2D—Variations of pancreatic ductular drainage.

past 14 years (Fig. 1C). In the previous 12 months before being seen at the Lahey Clinic Foundation, she had been hospitalized on four occasions.

At operation, "slight edema" of the pancreas and surrounding tissues was reported. After administration of secretin, all pancreatic juice drained by way of the minor papilla. Sphincterotomy of the minor and major papilla and cholecystectomy were performed. No calculi were found.

Case 4:—A 22-year old man with diabetes was seen in February, 1976 for abdominal pain (Fig. 1D). Diabetes mellitus was diagnosed at age 12. He took 35 units of NPH and 15 units of regular insulin a day. The patient was first hospitalized in 1972 for abdominal pain and hyperamy-

lasemia. He was subsequently hospitalized on multiple occasions for ketoacidosis with and without abdominal pain and hyperamylasemia. For several months before referral, abdominal pain had been unrelenting.

At endoscopy, edema and erythema were discovered in the first portion of the duodenum. Ultrasonic scanning of the pancreas raised the question of a sonolucent area in the region of the pancreatic tail. Surgical exploration was advised but was declined by the patient.

In each patient, the major papilla was identified at endoscopy by its typical anatomic features. The papillary orifice was easily cannulated and a short, branching pancreatic ductular structure typical of a ventral pancreas was opacified (Figs. 1A, 1B, 1C and 1D). In none of our patients did this structure communicate with the main pancreatic duct. In one patient (Case 4), the common bile duct was filled by injection through a common channel.

Comment

The embryologic development of the pancreas involves two anlagen. A dorsal bud and a hepatic diverticulum arise from a region in the foregut, which is destined to become the duodenum. The dorsal bud develops into the major part of the pancreas comprising the cephalic head, body and tail. A ventral bud developing from the hepatic diverticulum gives rise to the caudal head and uncinate process (ventral pancreas) and is intimately associated with the common bile duct. Because of growth differentials in this area, the ventral bud together with the developing common duct rotates backward behind the duodenum. When this rotation is completed the original ventral bud comes to lie caudal and posterior to the dorsal pancreas. In most persons, the two anlagen and their ductal systems fuse and the main drainage channel is through the ventral pancreas (duct of Wirsung) and the major papilla (papilla of Vater).

As might be anticipated, variations in pancreatic ductal drainage patterns are encountered when deviations occur in this process. On the basis of a detailed postmortem study of the pancreas and biliary ductal systems, Millbourn[2] classified the variants into three types. In type 1, the common bile duct and main pancreatic duct form a common channel before entering the papilla of Vater; in type 2, these ducts enter separately on the papilla of Vater and in type 3, the main pancreatic duct drains through the duct of Santorini or the minor papilla, and the common duct drains through the papilla of Vater in association with a small duct draining the ventral pancreatic anlage (Fig. 2A). Millbourn[2] found type 1 in 85.5% of patients; type 2 in 5.5% and type 3 in 9%. In two-thirds of persons with type 3, no connection was found between the duct of Wirsung and the duct of Santorini (6% of the total).

Anatomically, the minor papilla and the orifice of the duct of Santorini is an attenuated structure when compared to the papilla of Vater and its corresponding ductal orifice. Considerable variation occurs here. A demonstrated duct of Santorini may not exist or it may be of such a caliber to serve as an alternate drainage channel (Figs. 2B and 2C). It is seldom possible to cannulate the minor papilla during endoscopy or operation. The finding of this congenital variant in ductular anatomy in this group of patients with idiopathic pancreatitis suggests that pancreatitis may have resulted from inadequate flow through the minor papilla.

While the sphincteric obstructive theory of the pathophysiology of alcoholic pancreatitis no longer seems tenable,[3] obstruction clearly plays a role in some nonalcoholic patients. Hence, pancreatitis results from migration of calculi through the common bile duct and papilla of Vater, from the presence of roundworms in the papilla of Vater and from surgical injury to the papillary mechanism. Robechek[4] reported three members of a family with hereditary relapsing pancreatitis with hypertrophy of the sphincter of Oddi in whom attacks of pain were alleviated after sphincterotomy.

We propose that pancreatitis may have developed in our four patients with pancreatic ductal variants because of hindered pancreatic flow through an attenuated duct of Santorini and its orifice at the accessory papilla.

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Clinical Vignette

Gastric Carcinoid Endoscopically Simulating Leiomyoma

Case Report and Review of the Literature

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A 23-year old black man is presented who had a gastric carcinoid which clinically, endoscopically and radiographically simulated a leiomyoma. The gastroscopic findings and clinical features of gastric carcinoids are reviewed.

Introduction

Carcinoids are uncommon tumors of the gastrointestinal tract. The most frequent sites of involvement in the gastrointestinal tract are in the ileum and appendix. Less than 5% of gastrointestinal carcinoids arise in the stomach.[1] By 1963, only 93 cases of gastric carcinoid had been reported.[2] Gastroscopic findings have been reported in several cases but no distinct endoscopic picture has emerged.[3]

The following case report describes the clinical, radiographic and gastroscopic features of a gastric carcinoid that presented as an ulcerated submucosal lesion resembling either a leiomyoma or a pancreatic rest.

Case Report

A 23-year old black man was admitted to the Jackson Memorial Hospital, Miami, FL, with a three-day history of maroon-colored stools and a one-day history of several episodes of hematemesis. The patient denied abdominal pain or wretching. There was no history of peptic ulcer disease, salicylate ingestion or alcohol consumption.

At the time of admission, physical examination was unremarkable except for maroon-colored stool. Vital signs were within normal limits and remained stable. A nasogastric aspirate revealed bright red blood. Laboratory evaluation was unremarkable except for a hemoglobin of 11.6 gm.% and a hematocrit of 34%.

Endoscopy, performed on the day of admission, revealed a 2.5 cm. ulcerated submucosal mass lesion on the greater curvature in the proximal antrum (Fig. 1). Gastroscopic biopsies revealed normal gastric mucosa. An upper gastrointestinal series performed on the second hospital day confirmed the size, location and submucosal nature of the mass (Fig. 2). A tentative diagnosis of either ulcerated leiomyoma or pancreatic rest was made.

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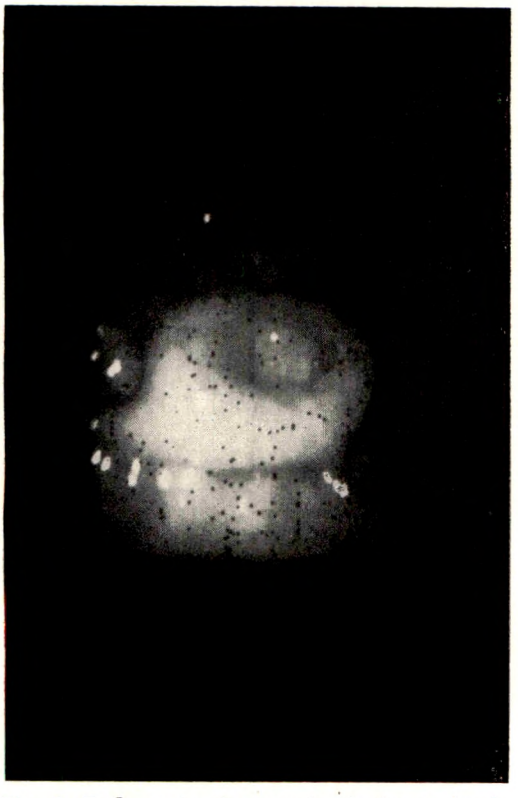


Fig. 1—Endoscopic photograph of ulcerated submucosal lesion in antrum of stomach.



Fig. 2—Upper gastrointestinal series revealing ulcerated submucosal lesion on greater curvature in antrum.

On the fifth hospital day, due to persistent hematemesis, an exploratory laparotomy was performed. Frozen sections taken from the lesion revealed a carcinoid tumor. A subtotal gastrectomy and Billroth II anastamosis was performed. No evidence for metastasis could be found at the time of surgery. An hematoxylin and eosin stain as well as a Fontanna-Masson silver stain revealed an argentaffin negative carcinoid tumor (Fig. 3). The patient has an uneventful postoperative course and was discharged asymptomatic on the 14th hospital day.

Comment

Symptoms of gastric carcinoid are nonspecific. Epigastric pain that is not relieved by antacids is the most common complaint.[4] Other symptoms include weight loss, nausea and vomiting. Because of the association with peptic ulcer disease, the presenting symptoms are often related to the ulcer diathesis.[5] Carcinoids in the stomach ulcerate more frequently than elsewhere in the gastrointestinal tract due to the acid-peptic environment. Any degree of blood loss can occur varying from asymptomatic melena to gross hematemesis. Gastric carcinoids frequently bleed regardless of size.[6] Honig and Weingarten have described massive gastrointestinal bleeding in association with a 1 cm. ulcerated gastric carcinoid.[7] Since carcinoid tumors of the foregut elaborate 5-hydroxytryptophane and histamine but not serotonin, the carcinoid syndrome has been reported in only eight of 90 cases of gastric carcinoid.[7]

Radiographically these lesions are most often round, small, sharply circumscribed, polypoid or submucosal filling defects.[8]

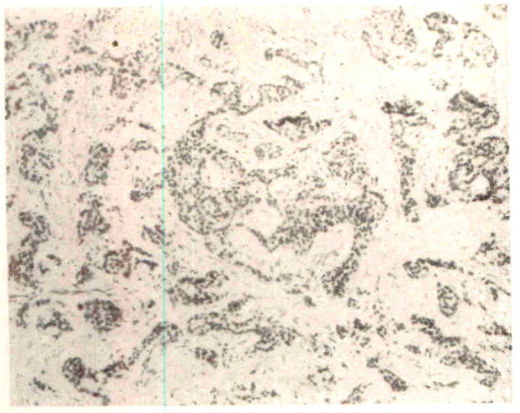


Fig. 3—Fontanna-Masson silver stain of resected specimen (original magnification x300).

Lesions to be considered in the differential diagnosis include pancreatic rest, polyps, leiomyoma, fibromas and polypoid carcinoma. They may occur anywhere within the stomach but are more common on the lesser curvature in the antrum, corresponding to the distribution of the Kultschitsky cells.[9] A central ulceration may be present depending on whether or not bleeding has occurred. In none of the cases studied in one series was the correct diagnosis made by x-ray alone.

Endoscopic observations have been reported only occasionally. Christodoulopoulos and Klatz reported the endoscopic findings in one case of their own and the four previous cases that had been gastroscoped up to that time.[3] One case presented with gastrointestinal bleeding and a gastric ulcer was identified. In the other cases, the gastroscopic diagnoses were nodular mass, benign tumor, antral polyp and ulcerated polypoid mass. The authors concluded that there was no distinct gastroscopic picture for carcinoid tumor in the stomach.

Gueller and Haddad have reported two cases of gastric carcinoid which had the endoscopic appearance of benign gastric polyps.[10] In both cases the diagnosis was made by endoscopic biopsy.

Our case was diagnosed radiographically as a 2 cm. ulcerating submucosal lesion, consistent with either leiomyoma or pancreatic rest. The endoscopic findings of a 2.5 cm. submucosal lesion with central ulceration were consistent with either of these diagnoses. Leiomyomas of this size, however, rarely cause significant gastrointestinal symptoms. Consequently the differential diagnosis of an ulcerated, bleeding, polypoid or submucosal lesion, especially if it is less than 3 cm., should include gastric carcinoid. Since carcinoids are true malignancies, with up to a 50% incidence of metastasis, early diagosis is essential.[11] Due to the nonspecificity of the x-ray findings and the rarity of the carcinoid syndrome in association with foregut carcinoid tumors, endoscopic evaluation with biopsy of all submucosal lesions may result in earlier diagnosis of these tumors.

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Clinical Vignette

Laparoscopic Diagnosis of Low Dose Radiation-induced Hepatitis

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A case of moderately severe radiation hepatitis resulting from low dose hepatic irradiation is presented. Clinical and histological features of radiation hepatitis are reviewed. In addition, the value of laparoscopy in the differential diagnosis of this entity is discussed.

Introduction

Radiation hepatitis is a well established but infrequently reported complication of radiotherapy. The clinical presentation, histological correlation, and critical dose levels have been well defined in previous publications.[1-4] We present a case of moderately severe radiation induced liver injury resulting from the administration of 2,300 rads, the lowest dose ever reported, along with the first laparoscopic description of the acutely injured liver following irradiation.

Case Report

A 58-year old, Caucasian male underwent A-P resection of the colon for Duke's stage B_2 adenocarcinoma of the rectum on 19 October 1976. At the time of operation, the surgeon noted a 2 mm. "nodule" on the anterior surface of the liver but did not perform a biopsy. A liver-spleen scan, obtained postoperatively, was normal. The patient subsequently received 4,500 rads to the pelvis over a five-week period. Prophylactic irradiation of the liver was also given as the "nodule" along with a slightly elevated alkaline phosphatase suggested hepatic metastasis. Treatments were stopped three weeks following the administration of 2,300 rads due to the development of thrombocytopenia. At this time, the patient noted gradually increasing abdominal girth, ankle edema, anorexia, lethargy, chills and dark urine. A liver-spleen scan on 23 February 1977 showed a dramatic change from the normal study done four months earlier. There was marked reduction of isotope uptake throughout most of the liver except for the inferior tip of the right lobe (Fig. 1). Physical examination revealed an afebrile, slightly cachectic man. There was a well healed mid line scar and left lower quadrant colostomy stoma. The liver was palpable 5 cm. below the right costal margin with a span of 15 cm. It was nontender and without nodules. The spleen was not palpable. Shifting dullness and fluid waves were noted. The remainder of the physical examination was unremark-

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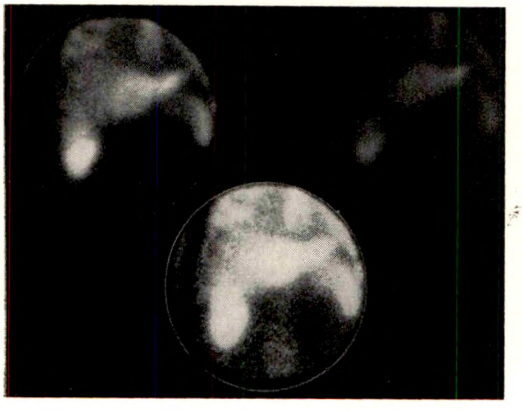


Fig. 1—Anterior ^{99m}TC scans showing nonhomogenous uptake of isotope in the liver and bone marrow one month postirradiation.

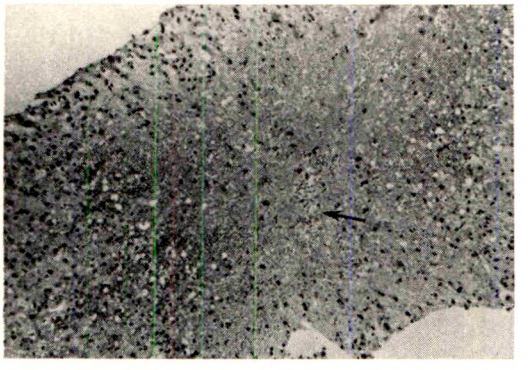


Fig. 3—Photomicrograph of centrolobular liver congestion with marked sinusoidal dilatation (arrow) (Hematoxylin and eosin, original magnification x100).

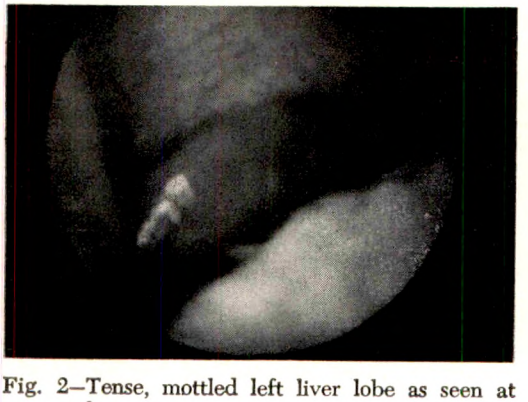


Fig. 2—Tense, mottled left liver lobe as seen at laparoscopy.

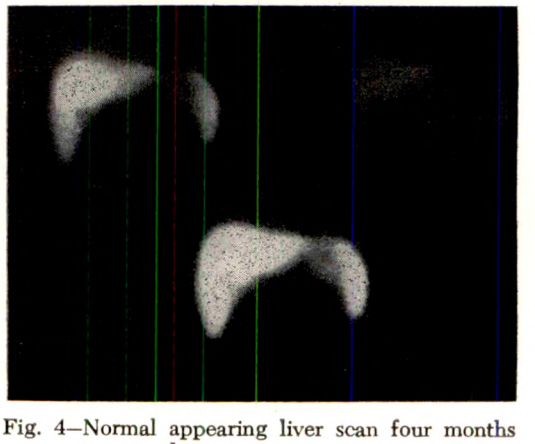


Fig. 4—Normal appearing liver scan four months postirradiation.

able except for pitting edema of the lower extremities. Laboratory evaluation included normal electrolytes and blood chemistries with the exception of a total protein of 5.4 gm./dl. and albumin of 2.8 gm./dl. The total bilirubin was 3.2 mg./100 ml. The LDH was 174 I.U.; alkaline phosphatase, 235 I.U.; SGOT, 122 I.U. Tumor markers and Hb_sAg were absent. Paracentesis fluid was consistent with a transudative process. Cytological examination was normal. Decision to perform a laparoscopic directed needle biopsy of the liver was made in order to rule out hepatic metastasis. The peritoneum and abdominal cavity appeared normal, however, the liver was noted to be tense, swollen, reddish-purple in color, with a finely irregular surface (Fig. 2). A needle biopsy was obtained which showed marked congestion and dilatation of the sinusoids most pronounced around the central veins (Fig. 3). Areas of focal interstitial fibrosis and necrosis were observed. Postoperatively the patient developed abdominal wall cellulitis and right-sided pleural effusion. He was treated with cephalothin, garamycin, clindamycin and discharged on the 28th hospital day. At outpatient follow-up, he is doing well with marked improvement of liver tests except for persistently elevated alkaline phosphatase. Repeat liver-spleen scan done three months subsequent to the initial abnormal

scan shows complete resolution of the radiation changes (Fig. 4).

Comment

Radiation-induced hepatitis usually develops two to six weeks postirradiation with complaints of weight gain and increasing abdominal girth. On physical examination hepatomegaly, ascites and jaundice are commonly found. Laboratory studies reveal abnormalities of most liver function tests, particularly elevation of the serum alkaline phosphatase.[1] The characteristic histological findings consist of centrolobular hemorrhage and sinusoidal congestion with adjacent cellular atrophy thought to be related to progressive fibrous obliteration of small branches of the hepatic veins.[2] Although the syndrome was first described in 1925,[3] it remains an infrequently reported entity despite current use of whole liver irradiation.

Safe but effective doses have been a topic of concern since reports of injury to the liver were first described. Although the liver had been thought to be a relatively radio-resistant organ, it is now recognized to be one of the most radio-sensitive, second only to bone marrow, lymphoid tissue, germinal tissue and kidney.[1, 4] Ingold, et al,[1] in a series of 40 patients, documented not only the liver's vulnerability to radiation but also established a dose dependent relationship. Their work, followed by a number of other studies,[5-8] led to the conclusion that 3,000 r over three to four weeks was safe, but as exposure increased, so did morbidity and mortality. Although three cases of minimal hepatic injury subsequent to low dose irradiation have been reported (2,500-2,700 r), more serious complications are generally reserved for those patients receiving greater than 3,500 r.[9]

The clinical presentation of radiation hepatitis often suggests recurrent neoplasia. Biopsy is the definitive diagnostic procedure but blind biopsy alone is not sufficient to exclude tumor. Many reports exist correlating the histological and clinical features of radiation hepatitis, however, only one *in vivo* gross description of the liver can be found. In 1968, Lansing, et al performed a minilaparotomy with open liver biopsy on a patient found to have radiation hepatitis. They reported a tense, mottled, purple liver not unlike that which had previously been described at necropsy and consistent with what we observed at laparoscopy. Perhaps the best description of gross changes in the liver after irradiation were reported by Reed and Cox in their series of 17 cases examined at autopsy.[2] When liver specimens were studied within 100 days following completion of treatment, marked hyperemia with a mottled pattern was observed suggesting prominent involvement of lobular centers. Specimens obtained within 25 days had no gross changes.

Isolated organ irradiation is currently a popular mode of cancer therapy. Even though 3,000 r has been established as a safe and effective dose, the individual patient's susceptibility to tissue injury cannot be ignored. Our patient not only acquired radiation induced hepatitis but, moreover, sustained injury at a dose of 2,300 r. This is the lowest reported dose to be associated with extensive liver injury. In addition, the laparoscopic findings provide us with the first complete description of the acutely injured liver *in vivo*. Laparoscopy should be considered a valuable diagnostic tool in differentiating recurrent hepatic tumor from radiation induced liver disease.

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Clinical Vignette

Hepatic Injury Due to Oxacillin Administration

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Hepatotoxicity, in association with intravenous oxacillin therapy, is described and documented for the first time by liver biopsy in an illicit drug user suffering from acute staphylococcal endocarditis. Mild gastrointestinal symptomatology, fever, eosinophilia and abnormal liver enzyme abnormalities were noted. Liver biopsy showed features consistent with a drug-induced hepatic injury. Cessation of therapy led to rapid reversal of clinical and biochemical changes and on further observation no evidence of chronic hepatic dysfunction was noted. A brief review of oxacillin hepatic injury is presented.

Introduction

Penicillin commonly causes hypersensitivity reaction but rarely produces hepatic injury.[1] Oxacillin, a synthetic penicillin, has been associated with transient elevations of serum transaminases during therapy,[2-4] apparently due to the release of muscle enzymes secondary to injury produced by the intramuscular administration of the agent. Freedman[5] described a patient with both hematologic and hepatic injury occurring during chronic oral oxacillin therapy. A reversible cholestatic form of hepatitis has also been described.[6] Most recently Dismukes[7] reported symptomatic biochemical hepatic dysfunction in three patients receiving intravenous oxacillin. Rapid reversal of both symptoms and elevated transaminases occurred after discontinuation of treatment.

We recently have seen an illicit drug user who demonstrated abnormal transaminases during the course of intravenous treatment with oxacillin for staphylococcal endocarditis. Herein, we report for the first time hepatocellular injury proven by biopsy associated with high dose oxacillin therapy. We believe that the clinical, biochemical and histopathological events document the hepatotoxicity of this agent.

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Case Report

M. W. a 21-year old drug abuser, developed an erythematous pruritic maculopapular rash six hours after intravenous injection of one spoonful of cocaine. Despite the use of cocaine and other drugs intravenously for the past six months, the patient denied any previous medical illnesses related to drug usage.[8] He received benadryl and prednisone with improvement of the rash; however, over the next several days he developed weakness, lethargy, increasing fatigue and diffuse myalgias. Anorexia, nausea and vomiting, diarrhea and the presence of fever and chills necessitated his admission to the hospital.

TABLE I

	SGOT n = < 45 U.	SGPT n = < 40 U.	% Eosinophils
Admission	122	312	0
Day 10 of Rx	29	62	6
Day 20 of Rx	202	273	8
Day 29 of Rx	388	806	15
Day 40 of Rx	16	41	0

Hepatitis B surface antigen negative repeatedly. CMV, toxoplasmosis, and mono spot test negative. Alkaline phosphatase and bilirubin determination were persistently normal.

Upon admission to the University of California at Los Angeles the patient had a temperature of 40.5°C. Physical examination revealed an ill young man with rigors and chills. Blood pressure was 130/80; pulse, 130. The skin was red and warm. Scattered axillary and inguinal lymphadenopathy was present. Examination of the lungs revealed a few rales over the right anterior chest and a grade 2/6 systolic murmur was noted at the lower left sternal border. Liver and spleen were not palpable and the hepatic span was 10 cm. by percussion. The right fourth proximal interphalangeal joint was swollen and tender. There were no stigmas of chronic liver disease.

Multiple blood, urine and synovial fluid cultures grew staphylococcus aureus. The patient was started on 12 gm. daily of intravenous oxacillin and gentamicin 150 mg. every eight hours intravenously for five doses. The patient's condition remained critical and on the sixth day of his hospitalization, intravenous gentamicin was reinstituted, 80 mg. every eight hours. Synergy had been demonstrated *in vitro* between gentamicin and oxacillin. The patient began to improve slowly and he became afebrile except for intermittent evening fevers up to 39° C. Multiple blood cultures were sterile.

On admission, the patient's liver chemistries were abnormal but these returned to near normal values after 10 days in the hospital (Table I). On the 12th hospital day the hepatic tests again were abnormal. Eosinophilia was noted and a low grade intermittent fever persisted. Mild nausea and anorexia were noted. A percutaneous liver biopsy was performed on the 29th hospital day. Oxacillin and gentamicin were discontinued and the patient was begun on 2 gm. Cefazolin intravenously every six hours. The liver tests returned towards normal and the patient became afebrile. He was discharged after 41 days of hospitalization. The patient was readmitted three months later again with staphylococcal endocarditis. Liver tests at this time were within normal limits, and no eosinophilia was noted.

Pathology

By light microscopy the liver showed an intact lobular architecture with a regular pattern of hepatic cords. Central hepatocytes were shrunken and the sinusoids dilated in these regions of the lobule.

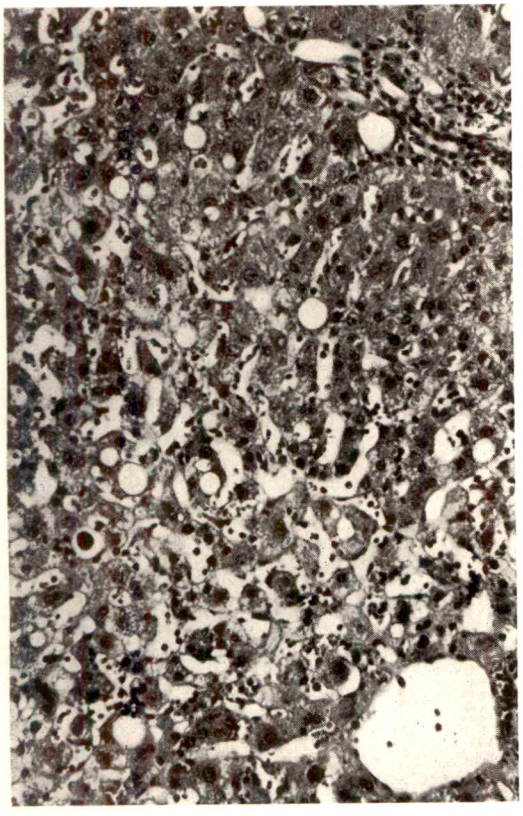


Fig. 1—The liver shows an intact lobular architecture with a regular pattern of hepatic cords. Central hepatocytes are shrunken and sinusoids dilated. Minimal fatty changes are present. Sinusoids and some triads contain neutrophils and lymphocytes with scattered eosinophilic bodies.

Minimal (1+) fatty metamorphosis was present (Fig. 1) and throughout the lobules evidences of necrosis with condensed hepatocytes and eosinophilic bodies were found. Sinusoids and some triads contained numerous neutrophils and lymphocytes. Electron microscopy confirmed the light microscopic observations.

Comment

Previous reports of oxacillin hepatic injury have been in patients receiving this medication orally[5, 6] or intramuscularly.[2, 4] In the latter, muscle injury seems to be the predominant source of the transaminase increase. Liver biopsy was not performed in Freedman's patient[5] and alternative explanations are present on review of this report. The patient described by Pas and Quinn[6] developed itching and jaundice after oral administration of oxacillin (76 gm.) which persisted 60 days after discontinuation of the medication. A liver biopsy showed a mild degree of bile pigment plugging in the canaliculus and intracellular bile pigment. No focal necrosis was present. The authors concluded that the clinical and pathological findings were compatible with a cholestatic hepatitis. Their patient differs from our experience and is probably not representative of the more common type of hepatic injury noted with this agent clinically.[7]

The case we described is the first in which liver biopsy documentation of hepatic injury secondary to oxacillin therapy is presented. This injury was manifested by rising transaminase levels in association with persistent fever, eosinophilia and mild gastrointestinal symptoms. Our patient had received a total of 180 gm. of oxacillin when his serum transaminases were noted to be abnormal. His biochemical manifestations of oxacillin hepatic injury seem quite similar to the previous patients described by Desmukes. In those patients, usually on or about the 10th-26th day of therapy with oxacillin, at a dosage of 8-10 gm. daily, nausea, vomiting and diffuse abdominal pain with temperature elevation and tenderness in the right upper quadrant developed. Following discontinuation of drug therapy there was rapid disappearance of symptoms, lysis of fever and a fall in the biochemical abnormalities.

Our patient was receiving no other therapeutic agents with known hepatotoxicity. We are not aware of any reports implicating gentamicin, although we can not exclude the possibility of drug interaction in this case. Indeed, it has been re-

ported that drug induced hepatic injury is more frequent among patients taking multiple drugs, than in those taking a single drug.[9] Thus, remotely, gentamicin may have contributed to the occurrence of hepatic injury in this patient.

Liver biopsy showed acute hepatocellular injury without evidence of cholestasis on the light microscopy, consistent with a drug induced hepatic injury.[10]

Alternative explanations for the hepatic lesions in this patient include congestive heart failure, endocarditis, viral hepatitis or the nonspecific hepatic dysfunction commonly seen in drug users.[11, 12] None of these are supported by clinical data, nor does the biopsy confirm these entities. Proof that oxacillin caused the hepatic injury would require rechallenge with this agent (a procedure which we were unwilling to perform). The hepatic injury noted in our patient did not cause any obvious chronic hepatic dysfunction. The rapid defervescence, reversibility of clinical symptoms and the abnormal hepatic function and eosinophilia upon discontinuation of oxacillin strongly argues for a drug induced liver injury. From the other reported cases as well as our patient the hepatic injury due to oxacillin suggests an idiosyncratic reaction with the temporal sequence supporting accumulation of a metabolic product.[13]

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Clinical Vignette

Ectopic Gallstone as a Cause of Gastric Outlet Obstruction

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Gallstone ileus is, of course, a well known cause of small bowel obstruction. A gallstone, however, is a very rare cause of gastric outlet obstruction. Three cases illustrating this phenomenon are exhibited. Radiographs were diagnostic in two of the studies. All three patients did well postoperatively.

Gallstone ileus is a well recognized cause of small bowel obstruction in the elderly patient. It accounts for from 1-3% of all small bowel obstructions.[1, 2] The site of impaction is usually the distal ileum (57-65%).[3-5] Impaction of a gallstone in the duodenum is unusual and may be responsible for gastric outlet obstruction. Several cases are presented with the radiographic findings.

Case Reports

Case 1:—J. S., a 52-year old female was admitted with a one week history of progressive abdominal distention, pain and nausea. She had undergone an oral cholecystogram in the past in which the gallbladder did not visualize. Physical examination revealed abdominal distention without localizing signs. A film of the abdomen (Fig. 1) revealed massive gastric distention and a contrast confirmed an obstruction (Fig. 2). At surgery the patient was found to have perforation of the gallbladder with a 3.2 × 2.2 cm. gallstone impacted in the first portion of the duodenum. After stone removal, pyloroplasty and cholecystectomy, she was discharged uneventfully.

Case 2:—J. M., a 65-year old male was admitted because of nausea, vomiting and epigastric pain of four days' duration. He had low grade fever with epigastric tenderness. An upper gastrointestinal examination showed a large filling defect in the duodenal bulb (Fig. 3). A later upper gastrointestinal examination showed a biliary-duodenal fistula (Fig. 4). Surgical exploration revealed the fistulous tract and a large gallstone lodged in the duodenal bulb. He left the hospital in good condition.

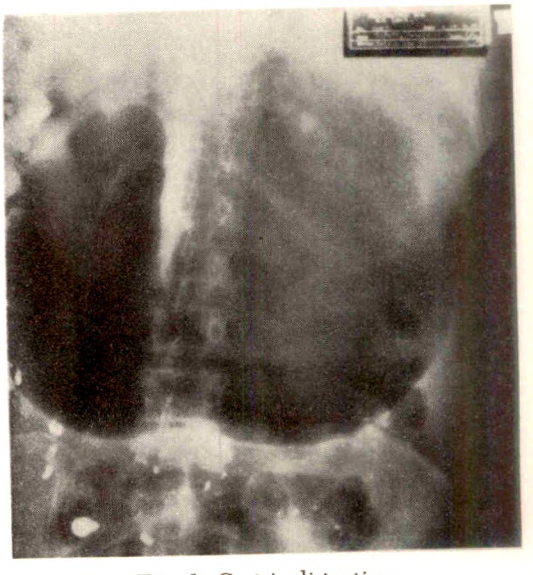


Fig. 1—Gastric distention.

From the Department of Radiology, Loyola University Medical Center.

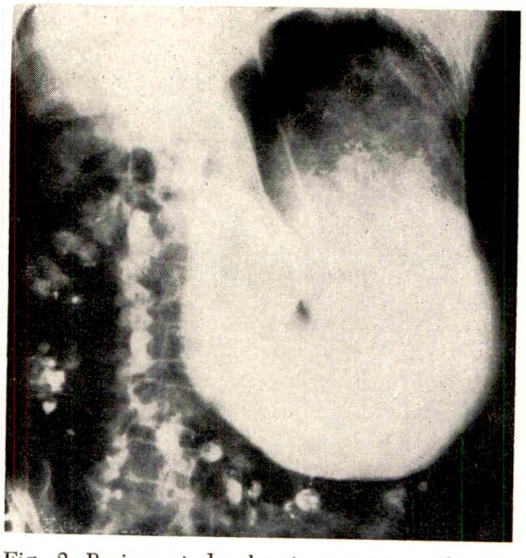


Fig. 2—Barium study showing gastric outlet obstruction. Colonic barium is from previous enema.



Fig. 3—Round filling defect in the duodenal bulb.

Case 3:—D. H., an 84-year old male was seen for upper gastrointestinal bleeding. Upon admission he has a history of nausea and vomitting for one day. Vital signs are stable. Hgb. was 9; Hct., 27.1. Pneumobilia was evident on plain films (Fig. 5). An upper gastrointestinal examination showed a deformed bulb with an ulcer crater and a tract of barium extending from the proximal duodenum to the cystic

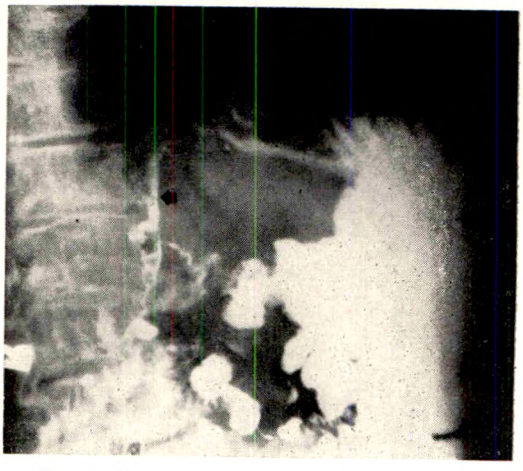


Fig. 4—Contrast entering the biliary tree.

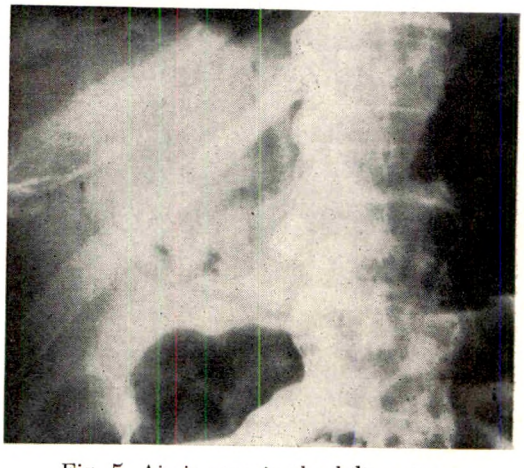


Fig. 5—Air is seen in the biliary tree.

duct (Fig. 6). A rounded calcification was seen in the right upper quadrant which was felt to represent a porcelain gallbladder or calcified stone. He did well on conservative treatment but presented several weeks later with signs of gastric outlet obstruction (Fig. 7). A repeat gastrointestinal study (Fig. 8) revealed a large filling defect in the duodenal bulb with obstruction. The right upper quadrant calcification was no longer seen. At surgery, a 5 × 7 cm. gallstone was removed from the duodenal bulb. The site of fistulization into the duodenum was noted to be at the ulcer crater previously seen on the upper gastrointestinal examination. Following cholecystectomy, gas-

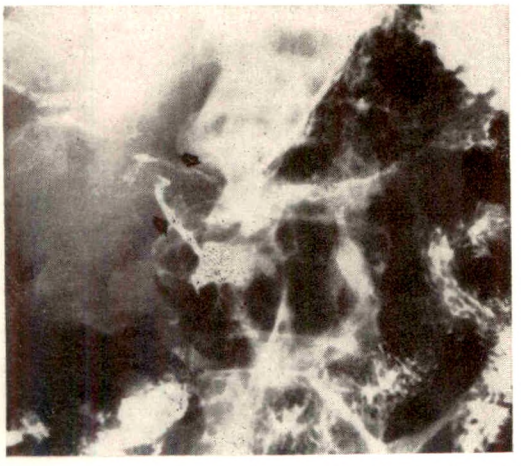


Fig. 6—Fistulous tract (arrow 1) from ulcer to cystic duct (arrow 2). Calcification (arrow 3) felt to represent calcified gallbladder or stone.

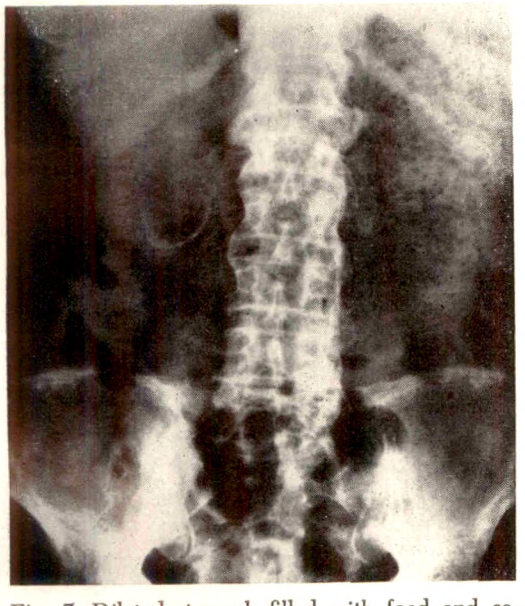


Fig. 7—Dilated stomach filled with food and secretions. Again note the rounded calcification in the right upper quadrant.

troenterostomy and fistula repair, the patient did well and was discharged uneventfully.

Comment

The classic radiographic triad described by Rigler[6] of pneumobilia, intestinal gallstone (which may change position on serial examinations) and distended loops of small bowel is almost pathognomonic of gallstone ileus, especially in the elderly. Although impaction in sites other than the ileum or jejunum is unusual, several cases have been reported, including the sigmoid, pylorus and duodenum.[2, 3, 7-12] In one series of 30 patients treated for gallstone obstructions of the small bowel, six had duodenal obstruction.[11] The pathogenesis is secondary to cholecystoduodenal fistula. This appears to result from an episode of cholecystitis with cholelithiasis. Inflammatory changes in the gallbladder bed then occur which results in adhesions between the gallbladder and adjacent duodenal wall. The gallstone then erodes by pressure to form the fistulous tract.[1, 5, 13] Even in cases where the stone lodges in the ileum, the most frequent site of perforation within the gastrointestinal tract is the duodenum.[1, 2] Depending upon the size of the stone, it may remain in the duodenum or pass distally until it encounters a narrower lumen. Although the inflammatory changes in the gallbladder itself create the fistula in most cases, a penetrating duodenal ulcer could be the initiating event as happened in our third patient.

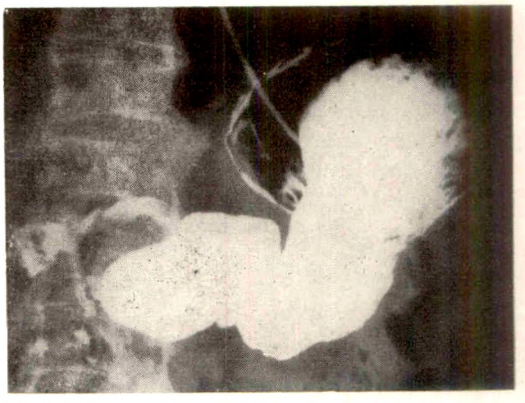


Fig. 8—Filling defect in region of duodenal bulb.

From a radiographic standpoint, a stone impacted in the duodenum may show

plain film findings of gastric dilitation, air in the biliary tract, or ectopic gallstone. Contrast films will demonstrate the obstructing stone and may show the fistulous tract.

Conclusion

Gallstone ileus is produced by passage of a stone through a cholecystoduodenal fistula in the majority of cases. Although unusual, impaction within the duodenum itself may occur and should be considered in the patient with signs of high intestinal obstruction. Barium studies will usually confirm the diagnosis.

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Clinical Vignette

Adrenergic and Cholinergic Innervation of the Supraduodenal Common Bile Duct

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The in-built intrinsic adrenergic and cholinergic nervous apparatus of the supraduodenal common bile duct of the cat and the dog was studied using modern selective specific neurohistochemical technics. A rich distribution of fluorescing varicose adrenergic axons and small nerve fascicles was observed within all layers of the duct. The cholinergic innervation was even more richly developed, including large nerve fascicles and nerve trunks as well as cholinergic nerve cells and small ganglia. The present observations corroborate the theory that the common bile duct actively participates, under dual neural control, in biliary dynamics and is not merely a passive conducting tube.

Introduction

Recent electrophysiological, pharmacological and cinéroentgenological studies on biliary dynamics have provided evidence that the common bile duct is not merely a passive conducting tube, but, through its own intrinsic activity, contributes to the function of the extrahepatic biliary tract.[1-4] There is also evidence that at least some of the biliary tract symptoms that occur after cholecystectomy may be related to functional spastic phenomena in the common bile duct,[5] although opinions on this are still somewhat divided.[4, 6] The common bile duct embeds and is surrounded by ganglionated nerve plexuses which obviously closely control the activity of the biliary smooth muscle through the ganglia which receive continuous information from multiple pressure receptors.[4, 7, 8] In addition, this nerve net obviously incorporates a direct nervous pathway between the gallbladder and the ampulla responsible for reciprocal reflex nervous activity of the gallbladder and the sphincteric region which may be blocked by grafting or cicatrization of the common bile duct, or by dividing the duct and its surrounding nerve plexus.[9-13] Cholecystectomy disrupts this nervous pathway and the trigger area in the collum region of the gallbladder is removed. This may explain why dilatation of the common bile duct often follows cholecystectomy, an observation first described by Oddi in 1887[14] and since then confirmed but also challenged several times.[15-17] Zanobio[18] emphasized the importance of the intrinsic ganglionated nerve plexuses in joining the extrahepatic biliary duct system, the choledochopancreaticoduodenal junction and the duodenum into a functional entity. The importance of the function of the intrinsic nervous system of the biliary tract is further accentuated by the observation that the release of cholecystokinin depends on a cholinergic mechanism with at least one synapse and a local anesthetic susceptible mucosal receptor. Also that the gallbladder motor response to cholecystokinin is mediated by stimulation of the duodenal pacemaker and requires intact ductal innervation in order to empty the bile effec-

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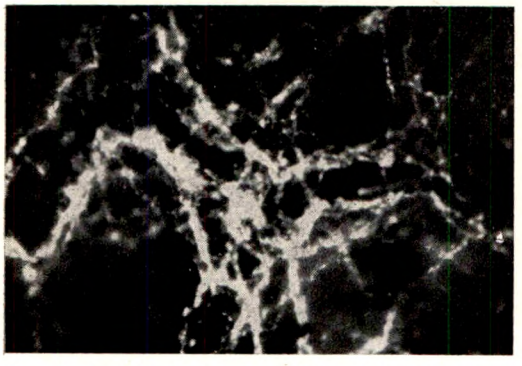


Fig. 1—A rich distribution of brightly blue-green fluorescing varicose axons within the wall of the supraduodenal common bile duct of the cat (GIF, original magnification x250).

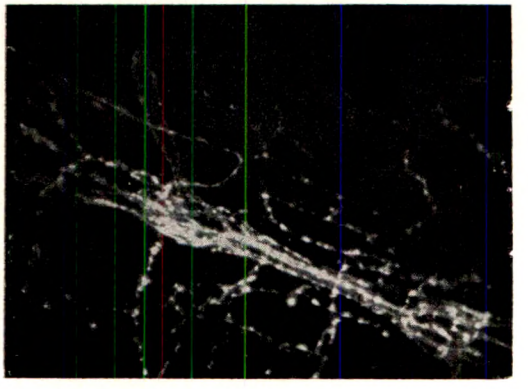


Fig. 2—A small-meshed three-dimensional net of single, brightly blue-green fluorescing delicate varicose axons and small fascicles, mainly coursing as "free" nerves (i.e. not related to the blood vessels) (Dog, GIF, original magnification x250).

tively,[6, 19] although this latter concept obviously has not been firmly established and is, in fact, not in agreement with the current view on mechanism of cholecystokinin on gallbladder. Thus, the in-built intrinsic nervous apparatus of the extrahepatic biliary duct system is for several reasons essential for normal biliary dynamics and involved in certain pathological conditions and has consequently been studied extensively using classical neurohistological stain technics.[7, 20-27] Surprisingly enough, studies based on modern neurohistochemical methods are few and contradictory and have not taken into account the cholinergic component of innervation. Such a study may therefore be of importance and interest.

Material and Methods

Five adult dogs and five adult cats were used for the present study. Under general anesthesia, small tissue specimens comprising the whole thickness of the supraduodenal common bile duct were excised and further processed for fluorescence histochemistry and cholinesterase histochemistry. The methods used were: A. Fluorescence histochemistry; 1. the formaldehyde-induced fluorescence histochemical method for freeze-dried specimens;[28] 2. the formaldehyde-induced fluorescence histochemical method for flat stretch preparations;[28, 30] 3. the glyoxylic acid-induced fluorescence histochemical method.[31, 32] In order to check the specificity of the fluorescence, reserpinization was performed on some control animals, resulting in the complete disappearance of the fluorescing nerves (2.5 mg./kg. body weight reserpine (Serpasil®, Ciba, Switzerland) was given intraperitoneally 24 hours before sacrifice to two cats and two cats received 3 × 3 mg. reserpine/kg. (30 hr., 8 hr. and 4 hr.) before sacrifice). B. Cholinesterase histochemistry: for the demonstration of the acetylcholinesterase enzyme activity, two thiocholine methods were used: 1. Gomori's modification[33] of the Koelle-Friedenwald technics;[34] 2. the "direct-coloring" copper ferrocyanide method introduced by Karnovsky and Roots.[35] In order to check the validity of the histochemical reaction, eserine (10^{-5}M) was added to both the preincubation and incubation media, to inhibit all cholinesterase activity and in addition, some tissue sections were incubated without substrate. All the control specimens were completely devoid of cholinesterase activity.

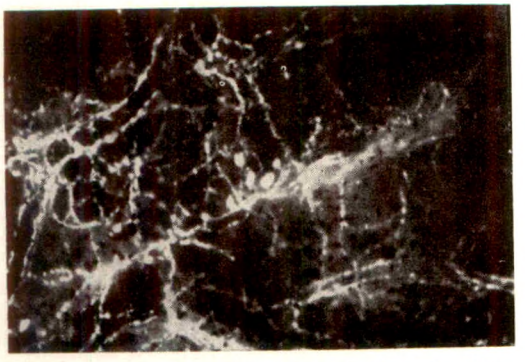


Fig. 3—A rich distribution of single, brightly blue-green fluorescing delicate varicose axons and small fascicles, obviously mainly "free" but some of them following the course of blood vessels as typical perivascular plexuses. The fluorescing cell bodies (arrows) in the middle of the figure are enterochromaffin cells in the epithelial lining of the common bile duct. In whole mount flat preparations (consisting of the inner half of the wall of the duct) the nucleus is not usually clearly identified because of the intense fluorescence of the surrounding cytoplasm. (Cat, FIF, original magnification x125). (Eränkö, et al.[30]).

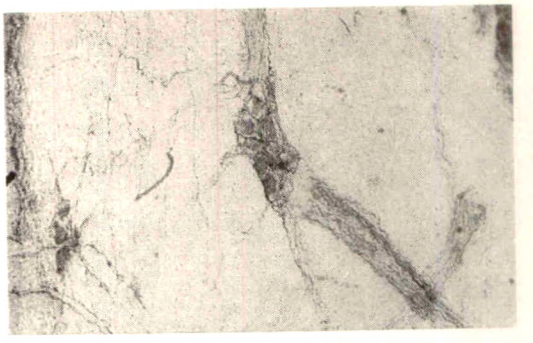


Fig. 4—A three-dimensional net of single acetylcholinesterase-positive axons and small fascicles within the muscular layer of the supraduodenal common bile duct of the dog. Branching nerve trunks with associated acetylcholinesterase-positive ganglia (arrows) are also seen. (Gomori's modification of the Koelle-Friedenwald thiocholine method, original magnification x125).

Results

Both in the dog and in the cat, a rich distribution of fluorescing varicose axons, running singly or gathered into small fascicles, was observed within all layers of the supraduodenal common bile duct (Figs. 1, 2 and 3). The blood vessels possessed the typical prominent perivascular nerve plexus but "free" (parenchymatous) nerves were also seen, in some parts even forming a dense three-dimensional nerve net (Figs. 1, 2 and 3). No fluorescing nerve cell bodies were observed. The results were identical in all three fluorescence histochemical methods used. Reserpinization resulted in complete disappearance of the fluorescing adrenergic nerves.

The cholinergic innervation, as studied by mapping the acetylcholinesterase-positive nerves and nerve cells, was even more richly developed. A small-meshed three-dimensional net of single varicose acetylcholinesterase-positive nerve fibers and small fascicles of them was observed within the wall of the supraduodenal common bile duct (Fig. 4). In addition, occasional large nerve fascicles or nerve trunks were also seen, with acetylcholinesterase-positive nerve cells or small ganglia of them at the crossing and branching points (Fig. 4).

Comment

The specificity and sensitivity of the fluorescence histochemical methods is now well documented.[31, 32, 36-38] All the fluorescing nerves seen are therefore adrenergic neural elements. This is further corroborated by the results of reserpinization, which resulted in the complete disappearance of the fluorescing nerves. An intense acetylcholinesterase reaction can be tentatively considered a criterion, if not definite proof, of the cholinergic nature of a neuron.[39] Thus, most of the acetylcholinesterase-positive nerves and nerve cell bodies are probably "truly cholinergic" neural elements, although the possibility cannot be excluded that some belong to the system of nonadrenergic inhibitory ("purinergic")

neurons.[40] To summarize, selective specific modern neurohistochemical methods have revealed and given confirmatory evidence for the existence of both adrenergic and cholinergic in-built intrinsic nervous apparatus within the wall of the supraduodenal common bile duct of the dog and the cat. There is no reason to assume that these sophisticated systems would have been developed without a functional necessity. Consequently, the results of the present study support the theory that the common bile duct actively participates, under dual neural control, in biliary dynamics and is not merely a passive conducting tube.

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Clinical Vignette

Cystosarcoma Phyllodes Metastatic to the Pancreas

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A case is presented of cystosarcoma phyllodes of the breast metastatic to the pancreas. Solitary metastasis to the pancreas has not been reported. The lesion was excised *in toto* with a good result. Clinical and pathological features of cystosarcoma phyllodes are discussed.

Although the pancreas is a frequent site of direct invasion from adjacent neoplasms, hematogenous metastases to the pancreas are uncommon. Most often, the primary malignancy originates in the lungs.[1] There has been only one previous case reported of cystosarcoma phyllodes metastasizing to the pancreas.[2] We recently treated a second patient who had such a metastasis.

Case Report

A 61-year old white woman was seen, complaining of backache of four weeks' duration. On physical examination an epigastric mass was discovered and she was admitted to the Mount Sinai Hospital Services, City Hospital Center at Elmhurst, in September, 1976. The patient denied having malaise, nausea, vomiting, or weight loss.

Her past history was remarkable in that in February, 1975 she had undergone a left simple mastectomy after a biopsy of a 4 cm. breast mass revealed cystosarcoma phyllodes. A chest x-ray, liver scan, and

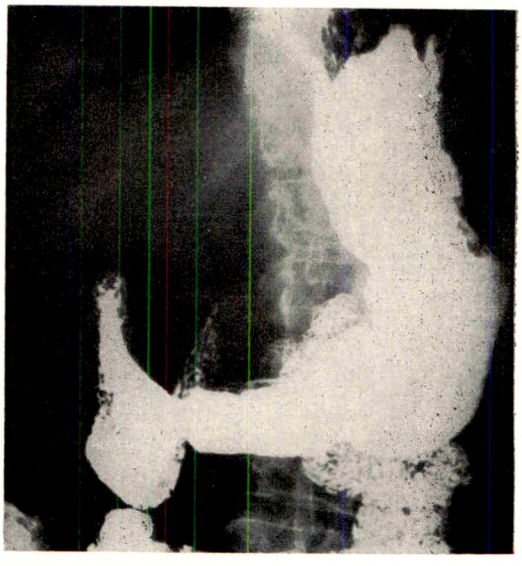


Fig. 1—Gastrointestinal series revealing mass displacing lesser curvature of the stomach downward.

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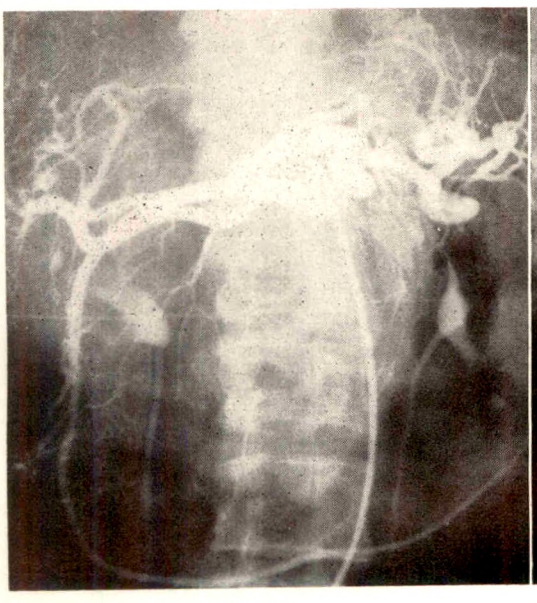


Fig. 2

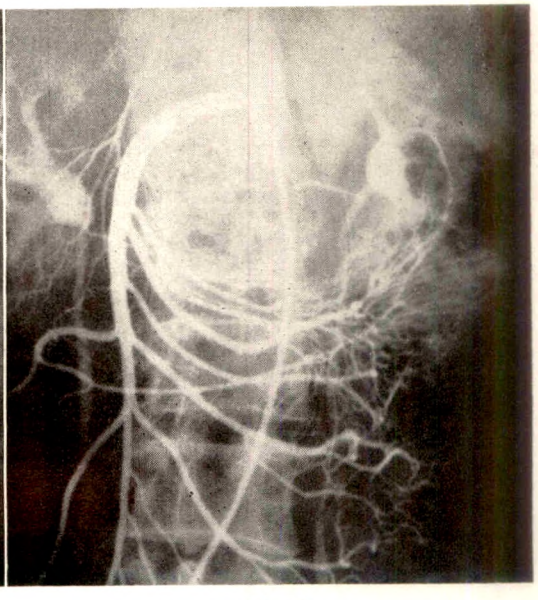


Fig. 3

Figs. 2 and 3—Celiac and superior mesenteric arteriograms revealing a large, avascular mass in the region of the pancreas.

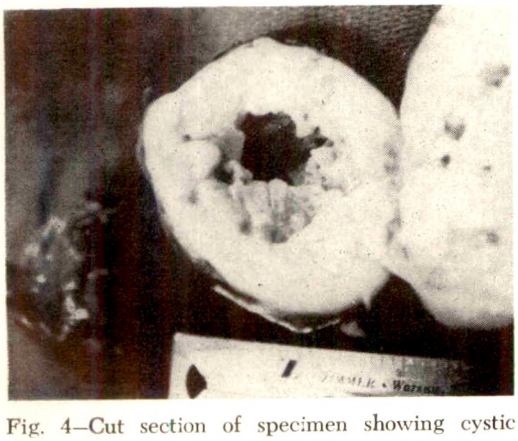


Fig. 4—Cut section of specimen showing cystic changes

bone scan failed to reveal any evidence of metastases.

At the present admission, the left mastectomy scar was well healed, with no evidence of local recurrence of the tumor. In the epigastric region there was a well defined, irregular, 10 cm., nontender, mobile, nonpulsatile mass. The mass did not move with respiration. The remainder of the physical examination was completely unremarkable.

Routine blood tests were within normal limits except for an elevated alkaline phosphatase of 208 I.U. (normal less 85). A chest x-ray was normal. A gastrointestinal series showed a retrogastric mass displacing the lesser curvature of the stomach anteriorly and downward (Fig. 1). A sonogram revealed a 6 × 8 cm. mass lesion in the pancreatic area with both cystic and solid components. A celiac and superior mesenteric arteriogram revealed a large, avascular mass in the region of the pancreas stretching but not encasing the vascular pancreatic arcade (Figs. 2 and 3). A spleen scan was normal. A bone scan revealed nonspecific changes in the skull and lumbar spine.

At laparotomy on 30 September a 10 × 10 cm., firm, well encapsulated mass was found arising from the body of the pancreas (Fig. 4). It encased the splenic vein and was adherent to the superior

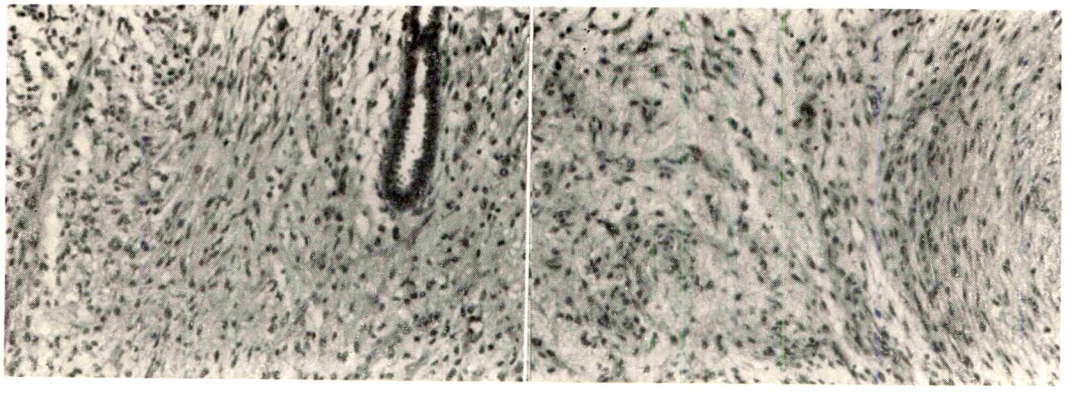


Fig. 5—*Left:* Breast tumor. *Right:* Metastases to pancreas.
In both a myxomatous stroma and bundles of spindle cells are seen. In the left figure, a mammary duct with well differentiated epithelium is present. Epithelial elements, however, were note present in the metastases.

mesenteric vein. The tumor and distal pancreas were excised in continuity. There was no evidence of tumor elsewhere in the abdomen.

On pathological examination, the tumor proved to be cystosarcoma phyllodes metastatic to the pancreas (Fig. 5). Several islet cells were found within the tumor tissue.

Six months after surgery the patient remains well, with no evidence of recurrent disease.

Comment

Willis collected 127 cases from the literature of tumors with hematogenous metastases to the pancreas.[1] In descending order of frequency, the primary malignancies responsible were carcinoma of the lung, melanoma, carcinoma of the kidney and carcinoma of the breast. Unlike our case, the secondary pancreatic tumors were usually small, well defined nodules that rarely produced clinical symptoms. Islet cells were often found to be intact within the substance of these tumors, as was the case in our patient's growth.

Cystosarcoma phyllodes is an uncommon neoplasm peculiar to the breast with both epithelial and connective tissue elements, differing from fibroadenomas by a pronounced overgrowth of the stromal element.[3] It has a low grade malignant potential, occasionally recurring locally after excision and less commonly producing blood-borne metastases. Regional lymph node involvement is rare. Some authors have attempted to predict the metastatic potential on the basis of histological appearance[3] but perhaps due to the marked pleomorphism which often exists, small foci of anaplasia may be overlooked even on multiple sectioning, and the correlation between histological features and biological behavior has proven unreliable.[2, 4]

The extent of initial resection probably influences the local recurrence rate but not the frequency of distant spread.[5, 6] Although controversial, most authors would perform a wide local excision or a simple mastectomy, resecting pectoralis muscle and excising axillary nodes only if they appeared to be involved.

When hematogenous metastases do occur, it is the mesenchymatous elements which are responsible, the epithelial elements playing a passive role.[7] The most frequent areas of seeding are the lungs

(66% of metastatic cases), bones (28.3%), heart (9.4%) and liver (5.6%). It appears that any abdominal organ may be involved, including stomach, omentum, kidney, adrenal gland, spleen, and para-aortic nodes.[4] Spread to the pancreas in the only other such reported case was one among multiple metastases.[2] The size of the pancreatic lesion and whether it was clinically recognized antemortem were not stated. Our patient had an easily palpable abdominal mass from a huge secondary pancreatic growth. There was no evidence of spread elsewhere.

The prognosis once distant metastases of cystosarcoma phyllodes have occurred is poor, few patients surviving beyond two years.[5]

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Clinical Vignette

Iron Deficiency Anemia from Afferent Loop Metastatic Hypernephroma Diagnosed by Endoscopy

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The natural history of renal cell carcinoma is unpredictable and clinical manifestations of the primary tumor and its metastases may be protean. Metastases from hypernephroma to the small and large bowel are uncommon.[1, 2] We report an unusual case of renal cell carcinoma which metastasized to the afferent loop; it produced iron deficiency anemia due to gastrointestinal blood loss. This lesion was diagnosed by fiberoptic endoscopy.

Case Report

N. G. S., a 60-year old white man, was admitted because of early satiety, weight loss and increasing weakness for three weeks prior to admission. There was no dysphagia, nausea or vomiting. During the two months before admission, he had noticed dark colored stools at times. There were no urinary complaints on this admission. About 10 years ago he underwent a partial gastrectomy and Billroth II anastomosis for bleeding peptic ulcer. One and a half years before this admission he developed right flank discomfort, hematuria, weight loss, right abdominal mass and right varicocele. Intravenous pyelogram and renal arteriogram confirmed the presence of right renal tumor. Right nephrectomy was performed; periaortic lymph nodes were found to be malignant but there were no hepatic metastases. Histologic examination showed it to be renal cell carcinoma. Physical examination on present admission showed normal vital signs, pallor of skin and conjunctivae, no lymph adenopathy. Liver was enlarged and hard; there was

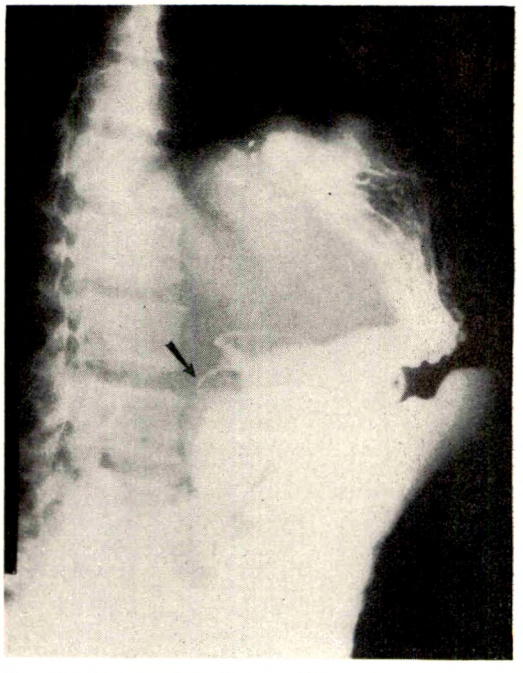


Fig. 1—Upper gastrointestinal series showing a mass in the duodenum.

Supported by the Medical Research Service of the Veterans Administration.

* Chief of Digestive Diseases and Nutrition (Gastroenterology). Louisville Veterans Administration Hospital; Associate Professor of Medicine, University of Louisville School of Medicine.

† Fellow in Digestive Diseases and Nutrition.



Fig. 2—Endoscopic view showing an ulcerated mass in the afferent loop.

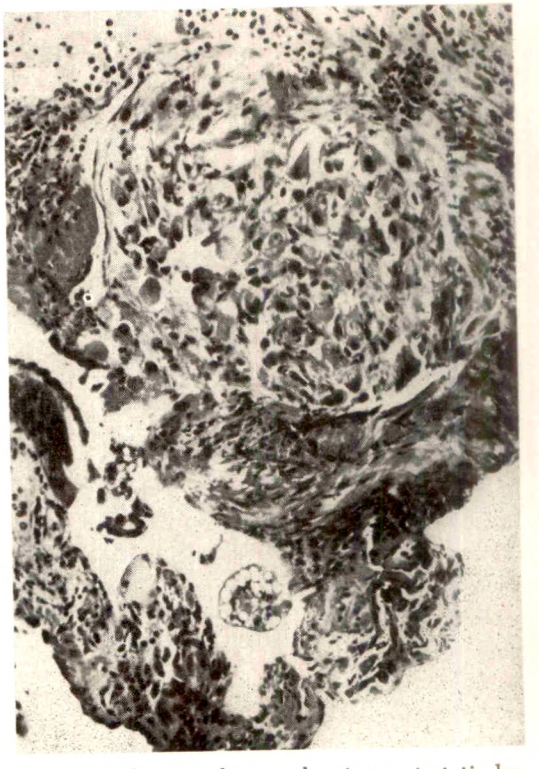


Fig. 3—Endoscopic biopsy showing metastatic hypernephroma (Hematoxylin and eosin, original magnification x250).

no splenomegaly. Hemoglobin was 8.8; hematocrit, 28.0; MCV, 83; MCH, 26.6; MCHC, 32. White blood cell count and platelets were normal. Stool guaic was repeatedly positive. Bone marrow examination showed reduced iron. Serum albumin was 2.3 and globulin 5.1. Serum protein electrophoresis suggested Waldenstrom's macroglobulinemia. Alkaline phosphatase was increased and on fractionation it was predominantly of hepatic origin. Prothrombin time, SGOT and SGPT were normal. A technetium liver scan showed multiple filling defects. Needle biopsy of the liver showed no evidence of malignancy. An upper gastrointestinal roentgenogram (Fig. 1) suggested a mass lesion in the duodenum. Fiberoptic esophagogastroduodenoscopy was performed. Details of the procedure and instrument have already been reported.[3] Esophagus, gastroesophageal junction, stomach and efferent stoma were found to be normal. In the afferent loop, a large (3 × 4 cm.) fungating, ulcerated mass was seen (Fig. 2). Biopsy performed by endoscope showed it to be a clear cell carcinoma compatible with metastatic hypernephroma (Fig. 3). The patient was started on chemotherapy.

Comment

Renal cell carcinoma may mimic many medical conditions because the metastatic sites are many and varied.[4, 5] The most common sites for metastases are lung and bone. Unusual sites of metastases reported are hernial sac, thyroid, vagina, esophagus, heart and colon.[4, 5] Small bowel metastases from hypernephroma are very rare.[6]

It is not unusual to miss hepatic metastases by needle biopsy of the liver and this patient probably has hepatic metastases.

It should be noted, however, that cases have been reported when liver scan, liver angiogram and liver function tests all suggested the presence of hepatic metastases but on laparotomy no hepatic metastases were found; on removal of the primary tumor, liver function tests became normal (nephrogenic hepatopathy).[6-10]

Gastrointestinal symptoms occur in about 20% of cases of hypernephroma[4, 10] but this fact is less well recognized. Anorexia, nausea, vomiting and abdominal distress are the symptoms often mentioned. Pressure from the primary tumor or local tumor ingrowth may be the basis of such symptoms. Low hemoglobin has been reported in 64% of cases[6] but the anemia is usually of normocytic normochromic type which occurs in many types of malignancy. Since bowel involvement by metastases is rare, gastrointestinal bleeding and iron deficiency anemia are not seen. The present case is unusual in that renal carcinoma produced a bleeding metastatic lesion in the afferent loop and it was definitively diagnosed by fiberoptic endoscopy.

Acknowledgment

We are grateful to Dr. W. Broghamer for interpreting the biopsy, to Ms. S. Fox for excellent secretarial assistance and to Mr. M. Howze for the photographs.

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Clinical Vignette

Sigmoid Stricture

An Unusual Presentation of Perforated Appendicitis with Abscess Formation

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Appendicitis is the most common acute surgical condition affecting the abdomen. The manner of onset and location of pain depend, to a great extent, upon the different anatomical positions of the appendix and its proximity to the parietal peritoneum which senses the location of the inflammatory process. When perforation occurs, abscess formation or diffuse peritonitis may develop. We wish to report an unusually rare case of perforated appendicitis with abscess formation presenting clinically and radiologically as a sigmoid stricture.

Case Report

The patient is a 32-year old white male who experienced diffuse lower abdominal cramping pain associated with constipation for two days prior to visiting his family practitioner. There was no fever, nausea, vomiting nor blood loss but slight abdominal distention was present. Survey films of the abdomen were normal. A barium enema x-ray study of the colon showed a 3 cm. long "stricture" at the sigmoid level although details were obscured because of inadequate cleansing of the colon and incomplete filling with barium. When repeated three days later, the finding was again that of a sigmoid stricture occurring about 45 cm. from the anus (Fig. 1). The colon was otherwise considered normal. A colonoscopic examination was performed as an outpatient with satisfactory visualization of the entire colon. The involved segment was described as a short area of "spasm" with normal mucosa, raising the possibility of an intramural or extralumenal cause. Four weeks after the initial visit the patient was entirely asymptomatic and in good health. Another barium enema x-ray series was performed showing essentially similar findings. At this time the patient was admitted to the hospital. There were no abnormal physical nor laboratory findings.

Colonoscopy was repeated with similar mucosal findings but inability to advance the colonoscope past the strictured segment. No intrinsic lesion was seen and multiple biopsies and cytologic studies were normal. An abdominal exploration was subsequently performed.

At surgery, the peritoneal cavity contained fibrinous adhesions between several loops of small intestine. The cecum was tented downward and an inflammatory mass was present in the pelvis involving the distal sigmoid colon on its right side

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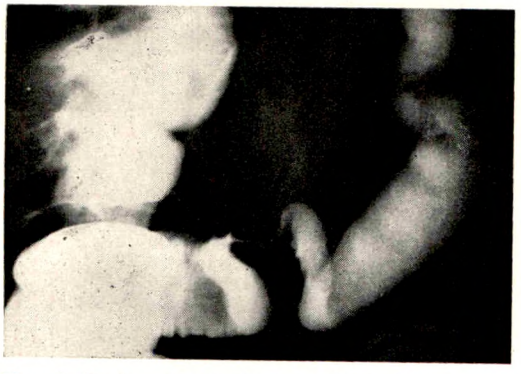


Fig. 1—Barium enema shows a sigmoid "stricture" about 45 cm. from the anus.

with the base of the appendix extending into the mass. A diagnosis of appendicitis with perforation and abscess formation was made and drainage performed. It was also possible to free-up the bowel and remove the appendix. No resection was needed. Culture of the abscess was taken which produced a growth of *E. coli* organisms. The patient made an uneventful postoperative recovery and was discharged from the hospital in satisfactory condition.

Comment

Acute appendicitis is a common surgical problem, with several well recognized modes of presentation usually related to the anatomical position of the appendix. When the appendix is wedged up in the pelvis and does not make contact with parietal peritoneum the usual findings may be absent and the diagnosis unsuspected for a considerable period of time while leakage and abscess formation occur. If the abscess is walled-off symptoms may completely subside until either resolution of the inflammatory process occurs or progressive phlegmon and abscess formation result in a new set of symptoms and signs. The phlegmon adjacent to the sigmoid colon in this case resulted in a mass causing extrinsic compression and irritability of the colon with a localized area of narrowing of the sigmoid colon during the asymptomatic period of the patient's illness.

A barium enema x-ray usually is not performed during acute appendicitis but is not contraindicated since the appendeceal lumen is obstructed and use of low pressure retrograde filling of the colon should not be expected to precipitate any complications.[1, 2] The findings supporting a diagnosis of acute appendicitis on barium study consist of a nonfilling appendix, mass effect on the medial and inferior borders of the cecum and mass effect or mucosal irregularities of the terminal ileum. Partial filling of the appendix with evidence of appendeceal mucosal abnormalities and mass effect in the ileocecal region can also be interpreted as findings suggesting appendicitis. Other conditions such as regional ileitis, acute diverticulitis of the ileum or cecum and Meckel's diverticulum may simulate the findings of acute appendicitis.

Our patient presented in an unusual manner with a prolonged clinical picture. The signs of a persistent inflammatory process such as fever, leucocytosis, elevated sedimentation rate were absent as well as a painful tender mass and symptoms of disturbed intestinal motility. Consequently, an accurate diagnosis could be made only at exploratory laparotomy.

Although rare, sigmoid stricture should also alert the physician to a point of origin elsewhere in the gastrointestinal tract when the onset of presentation appears to be unusual.

Acknowledgments

We are indebted to Dr. Fred Grose and Dr. Jacques Rosenfeld for allowing us to publish this case report.

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The Endoscopy Corner*

Acute Ulcerative Colitis Mimicking An Obstructing Carcinoma of the Colon

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Introduction

Inflammatory pseudopolyposis is one of the most common local complications of ulcerative colitis, being present in 10-20% of cases.[1] Pseudopolyps have been known to mimic neoplastic lesions often requiring surgical resection for differentiation.[2-5]

We have recently seen a patient with a partial obstruction of the sigmoid colon due to pseudopolyposis as part of the initial presentation of ulcerative colitis. Colonoscopy proved decisive in making the diagnosis of no malignancy and avoiding untimely surgery.

Case Report

A 49-year old white male was admitted to the hospital with bloody diarrhea. He had been in good health with no medical problems until two weeks prior to admission when he began to pass six to eight bloody, watery stools per day. He had no past history of colitis, denied any drug ingestion and had not traveled outside of the country. He had no abdominal pain, fever, chills or weight loss.

On physical examination he was a well nourished male in no acute distress. His blood pressure was 120/80 mm.Hg.; pulse, 70 beats/min. and temperature, 37.5° C. His abdomen was soft with normal bowel sounds and no visceromegaly. Rectal examination revealed no masses, fissures or fistulas; the stool was frankly bloody.

Sigmoidoscopy revealed edematous, friable, granular mucosa diffusely up to



Fig. 1—Barium enema examination demonstrates high degree of obstruction to the retrograde flow of barium.

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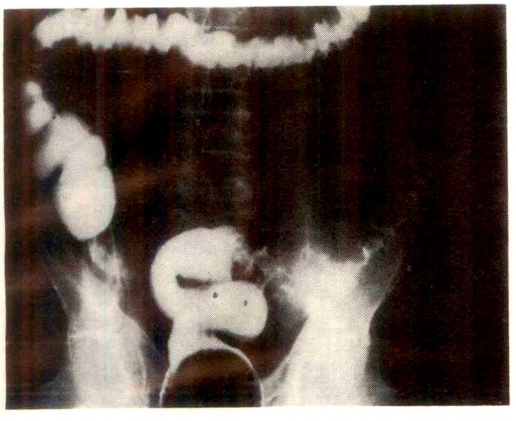


Fig. 2—Barium enema examination reveals diffuse ulcerations to the hepatic flexure and suspicious area demonstrating a "mass effect" in the area of sigmoid colon.

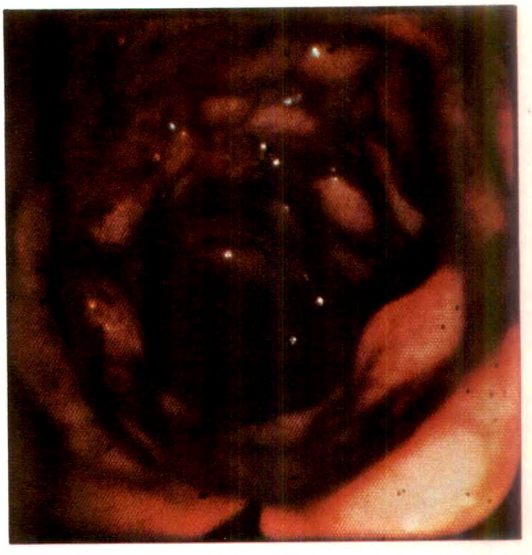


Fig. 3—Endoscopic picture demonstrating diffuse friability, edema and multiple pseudopolyps.

17 cm. where an obstructing lesion prevented further passage. The lesion was felt to be nodular although suboptimal visualization was obtained because of the friability. A biopsy of the obstructing lesion was obtained.

Initial barium enema examination failed twice (Fig. 1) to pass contrast agent beyond the obstructing lesion and the radiologist interpreted the finding as most compatible with carcinoma of the sigmoid colon. Because of the history, proctoscopic appearance and biopsy, which was consistent with pseudopolyps, a diagnosis of acute ulcerative colitis was made and the patient treated with Azulfidine®, prednisone and hydrocortisone enemas.

After three weeks the patient was experiencing only two to three bowel movements per day, which were partially formed without blood. A repeat barium enema (Fig. 2) showed changes of diffuse ulceration to the hepatic flexure but still the area of the previously obstructing lesion appeared suspicious and the concern of carcinoma remained.

Two weeks later a total colonoscopic examination using the Olympus CF-LB was performed. The area in question (Fig. 3) was diffusely involved by pseudopolyps. Multiple biopsies and cytology failed to reveal evidence of malignancy. The remainder of the colon to the hepatic flexure was involved by colitis but the ascending colon and cecum were grossly spared.

In light of the findings on colonoscopy, the patient was continued on tapering doses of prednisone and has continued to do well.

Comment

Ulcerative colitis presenting with the finding of a mass causing colonic obstruction is an unusual situation. Localized collections of pseudopolyps simulating obstructing neoplasms have been reported several times[5, 6] and the obstruction to the retrograde flows of barium has ranged from partial[5] to complete.[6] In all these previous cases the suspicion of malignancy had led to surgery and colonic resection.

It was once thought that inflammatory polyposis was related to the chronicity of

the disease. At present it is believed, rather, that the polyps are a consequence of the severity of the colitis. In one series, 8.8% of 204 patients had pseudopolyps at the time of their initial attack of colitis.[7] If the initial attack was severe, 30% were found to have pseudopolyposis.

Unlike the patients with giant pseudopolyps, the pseudopolyps in our case were not of great enough size to completely occlude the lumen and once the disease became more quiescent barium passed easily. This has led us to postulate that the obstruction was due to a combination of the large collection of pseudopolyps, edema secondary to the inflammatory state and spasm of the sigmoid colon. Although the pseudopolyps remained, control of the disease caused alleviation of the other problems and allowed a more successful contrast study.

In conclusion, we have presented a case of ulcerative colitis presenting initially with large pseudopolyps, edema and spasm which masqueraded as an obstructing carcinoma. Proctoscopic colonoscopic and anti-inflammatory therapy all played a significant role in altering the d obstructing carcinoma to ulc with pseudopolyposis.

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The Radiology Corner*

Segmental Ascending Retrocecal Appendicitis: The Significance of the Barium Enema

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Barium enema examination has again been advocated as a means of diagnosing acute appendicitis.[1] Visualization of the appendix on barium enema, once thought to totally exclude this diagnosis[2] must now be re-evaluated as to its significance. This communication points out the fallacy that either a normal cecum or appendiceal visualization on barium studies excludes acute appendicitis. The radiological findings of segmental retrocecal appendicitis are correlated with its pathological changes in this review.

Case History

A 27-year old white man was admitted to Jackson Memorial Hospital, Miami, FL with a one-day history of crampy, right upper quadrant pain associated with fever and chills without rigors. The pain was nonradiating, unrelated to meals and was not associated with anorexia, nausea or change in bowel habits. He had no previous history of abdominal pain. Systems review was unremarkable except for polydipsia and polyuria that had been present for several years. His maternal grandmother and uncle had diabetes mellitus.

Pertinent physical findings on admission revealed an obese white man in no acute distress with a temperature of 39° F; pulse, 104, regular and blood pressure of 140/84 mm. Hg. Chest examination revealed a regular sinus rhythm with a grade II/VI systolic ejection murmur, heard best at the lower left sternal border. His abdomen was protuberant but soft with decreased bowel sounds and right upper quadrant tenderness to palpation with no rebound. The liver spanned 14 cm. to percussion and the spleen was not palpable. Rectal examination revealed no tenderness or masses. Stool was hematest negative.

Pertinent laboratory data revealed a hematocrit of 43% and a WBC count of 21,200/cm. mm. with a marked left shift. The electrolytes, blood urea nitrogen, amylase and liver function tests were within normal limits. The fasting blood glucose was 316 mg./dl. Urinalysis revealed a 3+ sugar and moderate ketones. Urine sediment contained 0-3 WBC/HPF and 1-6 RBC/HPF.

Radiological examinations included a normal chest film and a supine film of the abdomen that demonstrated a nonspecific bowel gas pattern. Retrospective review of

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Fig. 1—Adjacent inflammatory mass with gas bubbles (open arrow) and visualization of appendix (closed arrow).

this film revealed scattered extraluminal bubbles localized to the right flank area.

Hospital Course

The initial clinical impression was cholecystitis in a newly diagnosed diabetic and preliminary treatment was initiated with intravenous ampicillin. On the day of admission, a normal gallbladder and biliary ducts were visualized by intravenous cholecystogram. Over the next 24-hour period, the patient's abdominal pain and right upper quadrant tenderness decreased in intensity. Abdominal palpation, however, revealed an ill-defined, tender mass in the right upper quadrant. The patient continued to be febrile with persistent leucocytosis despite continued antibiotic therapy.

Barium enema study on the second hospital day demonstrated a normal cecum and filling of the appendiceal lumen for approximately 2-3 cm. The haustral pattern in the posterolateral aspect of the ascending colon was altered by edema of the mucous membrane and irritability as a result of a presumed adjacent inflammatory mass (Figs. 1 and 2).

Surgical exploration revealed a pericolonic abscess involving the ascending colon secondary to a perforated retrocecal appendix. A right hemicolectomy with an end-to-end ileotransverse colostomy was



Fig. 2—Altered haustral pattern with edema.

performed. The patient had an uneventful recovery.

The resected tissues included 35 cm. of proximal colon and cecum and 20 cm. of distal ileum. Gross examination revealed a 16.5 × 10.0 cm. mass medially and slightly posterior to the cecum and proximal colon. The terminal 9.0 cm. of ileum was adherent to the wall of the mass. Sections through the mass revealed a friable, hemorrhagic and necrotic pericolic abscess. The ap-



Fig. 3

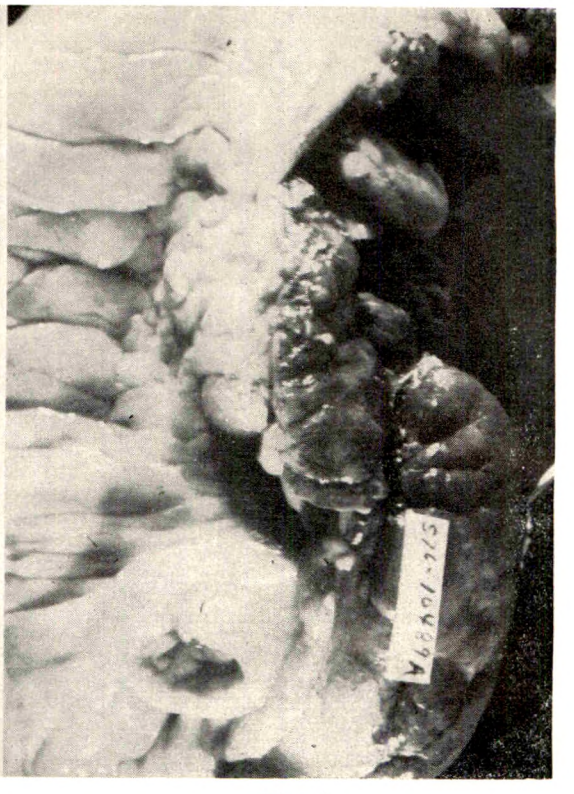


Fig. 4

Fig. 3—Proximal appendix showing normal lumen and mucosa. Muscular coat, serosa and mesoappendix thickened by young granulation tissue and cellular infiltrate (Hematoxylin and eosin, original magnification x4).

Fig. 4—Edematous cecal and ileocecal mucosa with adjacent hemorrhagic and purulent serositis.

pendix was identified with difficulty and found in a retrocecal position. It was 11.0 cm. in total length. The lumen, mucosa and submucosa of the proximal 7.0 cm. were normal though the muscular coat and serosa were moderately thickened by acute and chronic inflammation (Fig. 3). The appendiceal lumen distal to this point was obstructed. The remaining 4.0 cm. of the appendix was hemorrhagic, necrotic, enlarged to a diameter of 2.5 cm. and contained a 0.5 cm. perforation that communicated with the pericolic abscess. The mucosa of the colon and the ileum were edematous where contiguous with the abscess, but were otherwise normal (Fig. 3).

Comment

Barium enema studies have been employed increasingly as a diagnostic modality in patients with suspected acute appendicitis. Complete filling of the appendix with barium is felt to be a reliable sign of a normal appendix[3] since approximately 85% of normal appendices will fill with barium.[4] Unfortunately, the normal appendix varies in length from 4.0-12.0 cm.;[5] therefore, judging completeness of filling is difficult unless a previous visualization of the entire length is available for comparison. This case exemplifies the entity of segmental appendicitis which occurs when the appendiceal lumen is obstructed not at its

base but distally and the disease is localized beyond this obstruction. The proximal "normal" appendix, therefore, is visualized on barium studies.[3, 6]

In addition, the retrocecal position of the appendix occurs in as many as 65% of patients.[7] This anatomic position becomes clinically important as exemplified in our patient when this organ becomes acutely inflammed and gives rise to a wide variety of presenting signs and symptoms. Indeed, Collins found that only 142 of 751 patients (18.9%) with ascending retrocecal appendicitis presented with the classical symptoms and signs of acute appendicitis.[8] The diagnoses that can be simulated by a retrocecal appendicitis include inflammation of the gallbladder, liver, right lung base and genitourinary tract.

The roentgenographic features of ascending retrocecal appendicitis with abcess formation have recently been described.[9] These changes can involve the ascending colon from cecum to the hepatic flexure. The lateral or posterior haustral contour are specifically involved secondary to the adjacent appendiceal abscess. The wall exhibits nodularity and irregularity with associated spasm and narrowing of the lumen (Figs. 1, 2, 3 and 4). The sloping margins of this defect help its differentiation from colonic neoplasia.

The clinician must be aware that normal appendiceal visualization does not eliminate the diagnostic consideration of acute appendicitis. This visualization, when associated with the radiologic findings of a pericolic abscess should lead to earlier diagnosis and operative intervention with an attendant decrease in morbidity and mortality.

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The Last Page

Questions in Gastroenterology

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The Last Page appears as a regular feature in each issue of The American Journal of Gastroenterology.

The questions that follow have been prepared exclusively from material in the current issue of the Journal and the page on which the answer can be found is indicated with each question.

One way for regular readers of the Journal to utilize this feature is to scan *The Last Page* and attempt to answer the questions before reading the Journal. Then, when the articles have been read, return to *The Last Page*, again try to answer the questions and finally refer to the page locations that are provided in order to confirm your answers.

For each question, one or more responses may be correct, or none may be correct.

1. STUDIES OF THE EFFECT OF PROPRANOLOL ON INTESTINAL SECRETION HAVE SHOWN THAT:

   A. The intestinal inhibitory action of propranolol is site-specific to the colon.

   B. Propranolol completely inhibits deoxycholic acid and prostaglandin E_1 stimulation of colonic adenylate cyclase and net fluid secretion.

   C. While prostaglandin E_1 stimulates both small bowel and colonic adenylate cyclase and net secretion, only the effect on colonic secretion is affected by propranolol.

   D. Propranolol can be used to treat the diarrhea caused by cholera enterotoxin.

   (Page 134)

2. THE WATERY DIARRHEA SYNDROME HAS BEEN ASSOCIATED WITH:

   A. Pancreatic islet cell adenomas.

   B. Bronchogenic carcinomas.

   C. Pheochromocytomas.

   D. Ganglioneuroblastomas.

   (Page 139)

3. CONCERNING THE SUPERIOR MESENTERIC ARTERY COMPRESSION SYNDROME:

   A. It should be suspected in patients with chronic wasting diseases who are bedridden and have lost weight after which they develop frequent vomiting or aspirations.

   B. Gastrojejunostomy may relieve the gastric obstruction but not be adequate for duodenal obstruction.

   C. It may respond to intubation and keeping the patient supine in bed.

   D. Duodenojejunostomy is preferable to lysis of the ligament of Treitz and downward displacement of the duodenum as a means of relieving the obstruction.

   (Page 149)

4. THE PAROTID GLAND HAS BEEN SHOWN TO:

   A. Enlarge and hypersecrete in patients with chronic relapsing pancreatitis.

   B. Hyposecrete in nutritional deficiency states.

   C. Enlarge in patients with alcoholic cirrhosis.

   D. Atrophy in patients with duodenal ulcer disease.

   (Page 156)

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5. CONCERNING THE PANCREATIC DUCTS:

A. The common bile duct and main pancreatic duct form a common channel before entering the papilla of Vater in 15% of patients.

B. Acute relapsing pancreatitis may develop if an attenuated duct of Santorini is the dominant duct.

C. The duct of Santorini drains into the papilla of Vater.

D. No connection is found between the ducts of Wirsung and Santorini in 6% of patients.

(Page 162)

6. GASTRIC CARCINOID:

A. Accounts for less than 5% of gastrointestinal carcinoids.

B. Ulcerates more frequently than carcinoids elsewhere in the gastrointestinal tract.

C. Elaborates 5-hydroxyltryptophane, histamine and serotonin.

D. Is more common on the greater curve in the fundus.

(Page 165)

7. RADIATION-INDUCED HEPATITIS:

A. Usually develops two to six weeks post-irradiation.

B. Produces centrolobular hemorrhage and sinusoidal congestion with adjacent cellular atrophy due to progressive fibrous obliteration of small branches of the hepatic veins.

C. Rarely develops at levels below 3 000 r administered over three to four weeks.

D. Can be differentiated from recurrent hepatic tumor by laparoscopy.

(Page 169)

8. HEPATIC INJURY DUE TO OXACILLIN:

A. Occurs on or about the 10th-26th day of therapy at a dosage of 8-10 gm. daily.

B. On liver biopsy is seen to consist of intrahepatic cholestasis without significant hepatocellular injury.

C. Suggests an idiosyncratic reaction.

D. Is reflected by rising transaminase levels, eosinophilia, fever, mild gastrointestinal symptoms and right upper quadrant tenderness.

(Pages 172 and 173)

9. GALLSTONE ILEUS:

A. Accounts for from 1-3% of small bowel obstructions.

B. Is due to stone impaction in the distal ileum in 25% of cases.

C. Is produced by the passage of a stone through a cholecystoduodenal fistula.

D. May be caused by gallstone impaction in the duodenum.

(Page 178)

10. STUDIES OF THE INNERVATION OF THE COMMON BILE DUCT IN DOGS AND CATS SHOW THAT:

A. The duct functions as a passive conducting tube.

B. Varicose adrenergic axons and small nerve fascicles are observed within all layers of the duct.

C. Cholinergic innervation includes large nerve fascicles and nerve trunks.

D. Cholinergic nerve cells and ganglia are absent.

(Page 179)

11. SECONDARY NEOPLASTIC INVOLVEMENT OF THE PANCREAS:

A. Is most frequently by direct invasion from adjacent neoplasms.

B. Is most frequently by hematogenous metastases.

C. When hematogenous is usually from lung, melanoma, kidney or breast.

D. When hematogenous consists of small, well defined nodules that rarely produce clinical symptoms.

(Page 185)

12. RENAL CELL CARCINOMAS:

A. Commonly metastasize to the small bowel.

B. Can cause abnormal liver function tests in the absence of hepatic metastases (nephrogenic hepatopathy).

C. Cause gastrointestinal symptoms in 20% of cases.

D. Commonly cause a microcytic hypochromic anemia due to gastrointestinal blood loss.

(Page 190)

13. APPENDICITIS:

A. When suspected contraindicates the performance of a barium enema.

B. Is the most common acute surgical condition affecting the abdomen.

C. Can lead to abscess formation in the absence of fever, leucocytosis and an elevated sedimentation rate.

D. Can cause a sigmoid stricture by involving the distal colon in an inflammatory mass.

(Page 192)

14. INFLAMMATORY PSEUDOPOLYPOSIS:

A. Is a consequence of the severity of colitis not necessarily related to the chronicity of the disease.

B. Is present in 10-25% of cases of ulcerative colitis.

C. May masquerade as an obstructing carcinoma.

D. May be present at the time of an initial attack of colitis:

(Page 196)

15. BARIUM STUDIES OF THE APPENDIX REVEAL THAT:

A. A normal cecum or appendiceal visualization on barium studies excludes acute appendicitis.

B. Eighty-five per cent of normal appendices will fill with barium.

C. The normal appendix varies in length from 4-14 cm.

D. The retrocecal position of the appendix occurs in as many as 65% of patients.

(Page 200)

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PROGRAM

FORTY-THIRD
ANNUAL CONVENTION

AMERICAN COLLEGE OF
GASTROENTEROLOGY

SCIENTIFIC SESSIONS
25, 26, 27 SEPTEMBER 1978

AND

COURSE IN POSTGRADUATE
GASTROENTEROLOGY
28, 29, 30 SEPTEMBER 1978

THE MARRIOTT
DENVER, CO.

GENERAL INFORMATION

REGISTRATION—All members and guests should register. Identification badges for admittance to meetings will be given to those who register. These should be worn at all times during the session. Registration will take place at the registration desk on the convention floor. Registration facilities will open at 3:00 P.M. on Sunday and at 8:30 each morning.

LADIES REGISTRATION—At the registration desk on the convention floor. Registration facilities will open at 2:00 P.M. on Sunday and 8:30 each morning. Information concerning the various activities and events will be available there.

ANNUAL DINNER—Tickets will be sold by tables and will be available at the registration desk. Those desiring to be seated together must purchase tickets at the same time.

MEETINGS are held on local time and will begin promptly at the time specified.

COURSE IN POSTGRAUDATE GASTROENTEROLOGY—Admittance only upon presentation of official matriculation card.

SCIENTIFIC EXHIBITS will be in the Exhibit Hall and will be open Monday, Tuesday and Wednesday from 8:30 A.M. to 5:30 P.M.

TECHNICAL EXHIBITS under the direction of Steven K. Herlitz, Inc., Exhibit Managers, will be in the Exhibit Hall and will be open Monday, Tuesday and Wednesday from 8:30 A.M. to 5:30 P.M.

Those attending the Convention are urged to take advantage of the time in between the presentation of papers and sessions, to visit the technical exhibits and become acquainted with the many new products and new equipment on display.

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1969 Richard H. Marshak, M.D., F.A.C.G.: Ulcerative Granulomatous and Ischemic Colitis.

1970 Hans Popper, M.D., F.A.C.G. (Hon.): The Problem of Hepatitis.

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1973 Henry L. Bockus, M.D., F.A.C.G. (Hon.): The Doctor Image.

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1977 Joseph B. Kirsner, M.D., F.A.C.G. (Hon.): Some Biomedical Problems Presented by Inflammatory Bowel Disease.

1978 Charles S. Lieber, M.D., F.A.C.G.: Alcohol and the Liver: Progress Through 1978.

HENRY BAKER LECTURE

1974 F. Warren Nugent, M.D., F.A.C.G.: Crohn's Colitis Comes of Age.

1976 William M. Lukash, M.D., F.A.C.G.: Experiences as a White House Physician.

1977 Francisco Villardel, M.D., F.A.C.G.: Cytological Diagnosis of Digestive Cancer.

1978 John T. Galambos, M.D., F.A.C.G.: Surgery, Enzyme Kinetics and a Way of Life.

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1977 J. Edward Berk, M.D., F.A.C.G.: New Dimensions in the Laboratory Diagnosis of Pancreatic Disease.

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Membership in the College is open to all physicians, teachers and research workers whose interests lie in the field of Gastroenterology. If physicians they must be graduates of an accredited medical school, members in good standing, or eligible therefor, of their county and state medical societies and of the American Medical Association. If they are living in a foreign country, they must be members of a similar medical association in that country.

The major interest of the American College of Gastroenterology is to advance clinical gastroenterology. In addition, it also promotes and stimulates research, and teaching in gastrointestinal diseases and allied fields.

There are three (3) basic membership groups: (a) Member; (b) Associate Fellow; (c) Fellow.

For further information and membership application, write to the Secretary-General, American College of Gastroenterology, 299 Broadway, New York, NY 10007.

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12-18 October 1980

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Bal Harbour, FL
25-31 October 1981

BUSINESS AND SOCIAL SESSIONS

SATURDAY, 23 SEPTEMBER 1978

All Day

Various committee meetings at times to be arranged by committee chairmen—New Mexico Suite.

SUNDAY, 24 SEPTEMBER 1978

9:30 A.M.

Annual Meeting of the Board of Trustees—Nebraska Suite.

1:30 P.M.

Luncheon, Board of Trustees and Board of Governors—Salons G and H.

6:30 P.M.

Convocation—Salons D-F.

7:30 P.M.

Welcome Party—Ballroom Foyer.

8:30 P.M.

Buffet Supper—Salons D-H. Sponsored by William H. Rorer, Inc. (Admission by card only.)

MONDAY, 25 SEPTEMBER 1978

12:35 P.M.

Luncheon, Past Presidents—Wyoming Suite.

4:30 P.M.

Annual Meeting of the American College of Gastroenterology—Salon E.

TUESDAY, 26 SEPTEMBER 1978

7:30 A.M.

Annual Meeting and Breakfast of the Board of Governors—Wyoming Suite.

7:00 P.M.

Reception—Salons F, G, H.

8:00 P.M.

Annual Banquet and Dance—Salons D and E.

WEDNESDAY, 27 SEPTEMBER 1978

7:30 P.M.

Breakfast Meeting at the New Board of Trustees —Utah Suite.

SCIENTIFIC SESSIONS

FIRST SESSION

MONDAY MORNING,

25 SEPTEMBER 1978

WILLIAM S. ROSENTHAL, M.D., F.A.C.G., New York, NY, President, American College of Gastroenterology, presiding.

9:00 A.M.

Welcome—DR. ROSENTHAL

9:05 A.M.

1. **Progress Report on Controlled Trial of Fecal Occult Blood Testing for the Detection of Colorectal Neoplasia.**

SIDNEY J. WINAWER, M.D., F.A.C.G., New York, NY.

MARY GINTHER, B.A., New York, NY. (By invitation)

ERIC D. WESTON, M.D., New York, NY. (By invitation)

DANIEL G. MILLER, M.D., New York, NY. (By invitation), and

DAVID SCHOTTENFELD, M.D., New York, NY. (By invitation).

9:15 A.M.

Discussion.

9:20 A.M.

2. **Peritoneoscopy vs. Blind Biopsy in the Evaluation of Metastatic Cancer: A Controlled Comparison.**

JOHN A. DALE, M.D., Presidio of San Francisco, CA. (By invitation)

MELVIN L. BUTLER, M.D., F.A.C.G., Presidio of San Farncisco, CA., and

STEVEN T. HAYNE, M.D., Presidio of San Francisco, CA. (By invitation).

9:30 A.M.

Discussion.

9:35 A.M.

3. Early Detection of Adenomatous Hyperplasia of the Colon in Children with the Gardner Syndrome.

EMANUEL LEBENTHAL, M.D., F.A.C.G., Buffalo, NY., and

EDWIN W. NAYLOR, Ph.D., Buffalo, NY. (By invitation).

9:45 A.M.

Discussion.

9:50 A.M.

4. Metastatic Lung Carcinoma Involving the Gastrointestinal Tract.

JEFFREY J. RADIGAN, M.D., Martinez, CA. (By invitation)

EUGENE J. BURBIGE, M.D., Martinez, CA. (By invitation), and

JOSEPH P. BELBER, M.D., Martinez, CA. (By invitation).

10:00 A.M.

Discussion.

10:05 A.M.

5. The Nonmalignant Potential of Colonic Adenomatous Polyps.

ROBERT M. RICHTER, M.D., F.A.C.G., Brooklyn, NY.

LEON LITTMAN, M.D., F.A.C.G., Brooklyn, NY., and

ARTHUR ALLEN, M.D., Brooklyn, NY. (By invitation).

10:15 A.M.

Discussion.

10:20 A.M.

6. Presidential Address.

WILLIAM S. ROSENTHAL, M.D., F.A.C.G., New York, NY.

10:35 A.M.

Coffee break and recess to visit the technical and scientific exhibits.

11:05 A.M.

7. Early Gastric Cancer, Method of Diagnosis. Personal Experiences.

ERWIN SEIFERT, M.D., F.A.C.G., Koblenz, West Germany

H. BUTKE, M.D., Koblenz, West Germany (By invitation), and

K. GAIL, M.D., Koblenz, West Germany (By invitation).

11:15 A.M.

Discussion.

11:20 A.M.

8. Defect in Assimilation Following Combined Radiation and Chemotherapy in Patients with Locally Unresectable Pancreatic Carcinoma.

MARTIN H. KALSER, M.D., Miami, FL. (By invitation)

JAMIE S. BARKIN, M.D., F.A.C.G., Miami, FL.

DOROTHY REDLHAMMER, R.N., Miami, FL. (By invitation), and

M. HAAS, R.N., Miami, FL. (By invitation).

11:30 A.M.

Discussion.

11:35 A.M.

9. Observation of Arterial Vessels in Gastric and Duodenal Ulcers Not Actively Bleeding.

JOHN P. PAPP, M.D., F.A.C.G., Grand Rapids, MI.

11:45 A.M.

Discussion.

11:50 A.M.

10. Evaluation of Overt and Occult Gastrointestinal Bleeding: Analysis of 304 Patients.

FRANCIS J. TEDESCO, M.D., F.A.C.G., Augusta, GA.

JEROME D. WAYE, M.D., F.A.C.G., New York, NY.

JEFFREY B. RASKIN, M.D., F.A.C.G., Miami, FL.

RICHARD A. GREENWALD, M.D., F.A.C.G., Miami, FL., and

STEVEN J. MORRIS, M.D., Atlanta, GA. (By invitation).

12:00 Noon

Discussion.

12:05 P.M.

11. Value of Endoscopy in Infants and Children with Gastrointestinal Hemorrhage.

G. ODERDA, M.D., Chicago, IL. (By invitation)

FERNANDO VILLA, M.D., Chicago, IL.

MANUEL IGLESIAS, M.D., Chicago, IL. (By invitation), and

FREDERICK STEIGMANN, M.D., F.A.C.G., Chicago, IL.

12:15 P.M.

Discussion.

12:20 P.M.

12. Flexible Fiberoptic Endoscopy in Children and Adolescents.

PRESTON ZUCKER, M.D., F.A.C.G., Bronx, NY.

FREDRIC DAUM, M.D., Manhasset, NY. (By invitation)

G. DINARI, M.D., Bronx, NY. (By invitation).

S. KLEINHAUS, M.D., Bronx, NY. (By invitation), and

SCOTT J. BOLEY, M.D., Bronx, NY. (By invitation).

12:30 P.M.

Discussion.

12:35 P.M.

Past Presidents' Luncheon—Wyoming Suite.

SECOND SESSION

MONDAY AFTERNOON,

25 SEPTEMBER 1978

FRANZ GOLDSTEIN, M.D., F.A.C.G., Philadelphia, PA., Vice President, American College of Gastroenterology, presiding.

2:00 P.M.

PANEL ON NEW CONCEPTS AND APPROACHES TO GASTROINTESTINAL CANCER

Moderator

SIDNEY J. WINAWER, M.D., F.A.C.G., New York, NY.

Participants

13. Practical Chemotherapy of the Gastrointestinal Tract and Accessory Organs.

GEORGE E. MOORE, M.D., Denver, CO. (By invitation).

14. Experiences with Pion Radiotherapy.

MORTON M. KLIGERMAN, M.D., Albuquerque, NM. (By invitation).

3:00 P.M.

Question and Answer Period.

3:30 P.M.

15. Barrett's Esophagus and Chronic Duodenal Ulcer: An Important Clinical Association.

LUIS C. MAAS, M.D., F.A.C.G., Southfield, MI., and

EUGENE A. GELZAYD, M.D., F.A.C.G., Southfield, MI.

3:40 P.M.

16. Recent Experience with Barrett's Esophagitis and Peptic Ulceration of the Esophagus.

JOSEPH T. DANZI, M.D., F.A.C.G., Sayre, PA.

JOHN M. THOMAS, M.D., Sayre, PA. (By invitation).

BLAINE COBB, M.D., Sayre, PA. (By invitation), and

KENNETH MEYER, M.D., Sayre, PA. (By invitation).

3:50 P.M.

Discussion of papers 15 and 16.

4:00 P.M.

Coffee break and recess to visit the technical and scientific exhibits.

4:30 P.M.

ANNUAL MEETING of the American College of Gastroenterology—Salon E.

THIRD SESSION

TUESDAY MORNING,

26 SEPTEMBER 1978

SIDNEY J. WINAWER, M.D., F.A.C.G., New York, NY., Vice President, American College of Gastroenterology, presiding.

9:00 A.M.

17. Specificity of Elevated Amylase—Creatinine Clearance Ratio for Acute Pancreatitis.

EVANGELO FRIGAS, M.D., Morristown, NJ. (By invitation)

ELEFTHERIOS S. ANEVLAVIS, M.D., Athens, Greece (By invitation), and

JOSEPH J. RYAN, M.D., Morristown, NJ.

9:10 A.M.

18. Pancreatitis Caused by Bile Crystals Diagnosed by Biliary Drainage.

FRANZ GOLDSTEIN, M.D., F.A.C.G., Philadelphia, PA.

FRANK KUCER, M.D., Philadelphia, PA. (By invitation)

JAMES J. THORNTON, M.D., F.A.C.G., Philadelphia, PA., and

JOHN ABRAMSON, M.D., F.A.C.G., Philadelphia, PA.

9:20 A.M.

19. Further Studies Indicating a Direct Toxic Effect of Alcohol on Pancreatic Cells.

ORLANDO R. BORDALO, M.D., F.A.C.G., Lisbon, Portugal

MANUELA NORONHA, M.D., F.A.C.G., Lisbon, Portugal, and

DAVID A. DREILING, M.D., F.A.C.G., New York, NY.

9:30 A.M.

20. The Mechanism of Vasopressin Inhibition of Pancreatic Secretion.

PHILIP WOLFSON, M.D., New York, NY. (By invitation).

JOSEPH H. CORT, M.D., New York, NY. (By invitation), and

DAVID A. DREILING, M.D., F.A.C.G., New York, NY.

9:40 A.M.

21. The Effect of Acute Ethanol (Et) Intake on the Morphology of the Human Small Intestine.

IVAN T. BECK, M.D., F.A.C.G., Kingston, Ont.

MARIO S. MILLAN, M.D., Edmonton, Alta. (By invitation), and

GERALD P. MORRIS, Ph.D., Kingston, Ont. (By invitation).

9:50 A.M.

Discussion of papers 17-21

10:05 A.M.

22. Risk of Patient Exposure to an Oral Surgeon with HBsAG Acute Hepatitis.

STEPHEN C. HADLER, M.D., Phoenix, AZ. (By invitation), and

JAMES W. MANIER, M.D., F.A.C.G., Marshfield, WI.

10:15 A.M.

Discussion.

10:20 A.M.

23. Report of the National Commission on Digestive Diseases.

RICHARD G. FARMER, M.D., F.A.C.G., Cleveland, OH.

10:35 A.M.

Coffee break and recess to visit the technical and scientific exhibits.

11:05 A.M.

PANEL ON ENTERAL NUTRITION

Moderator

GEORGE L. BLACKBURN, M.D., Boston, MA. (By invitation).

Participants

24. Enteral Nutrition—An Overview.

GEORGE L. BLACKBURN, M.D., Boston, MA. (By invitation).

25. Enteral Nutrition in Trauma.

CHARLES W. VAN WAY, III, M.D., Denver, CO. (By invitation).

26. Enteral Nutrition Therapy for Colon Disease.

JOHN ROMBEAU, M.D., Martinez, CA. (By invitation).

12:05 P.M.

Question and Answer Period.

FOURTH SESSION

TUESDAY AFTERNOON,

26 SEPTEMBER 1978

F. WARREN NUGENT, M.D., F.A.C.G., Boston, MA., Past President, American College of Gastroenterology, presiding.

2:00 P.M.

DAVID C. H. SUN LECTURE

27. Radioimmunoassay in Gastroenterology.

ROSALYN S. YALOW, Ph.D., Bronx, NY. (By invitation).

2:30 P.M.

28. New Data on Successful Treatment of Crohn's Disease with 6-Mercaptopurine: A Double-blind Study and Subsequent Observation.

BURTON I. KORELITZ, M.D., F.A.C.G., New York, NY.

N. WISCH, M.D., New York, NY. (By invitation)

J. L. GLASS, M.D., New York, NY. (By invitation), and

DANIEL H. PRESENT, M.D., New York, NY. (By invitation).

2:40 P.M.

Discussion.

2:45 P.M.

29. Serum 25-Hydroxyvitamin D (25 OHD) Levels in Children and Adolescents with Inflammatory Bowel Disease (IBD).

FRED DAUM, M.D., Manhasset, NY. (By invitation)

A. R. FLEISCHMAN, M.D., Bronx, NY. (By invitation)

G. DINARI, M.D., Bronx, NY. (By invitation)

HARVEY AIGES, M.D., Manhasset, NY. (By invitation), and

J. F. ROSEN, M.D., Bronx, NY. (By invitation).

2:55 P.M.

Discussion.

3:00 P.M.

30. Long-term Prognosis for Patients with Ulcerative Proctosigmoiditis (Ulcerative Colitis Confined to the Rectum and Sigmoid Colon).

RICHARD G. FARMER, M.D., F.A.C.G., Cleveland, OH., and

GEORGE B. RANKIN, M.D., F.A.C.G., Cleveland, OH.

3:10 P.M.

Discussion.

3:15 P.M.

31. The Surgical Management of Ileosigmoid Fistula in Crohn's Disease.

TOMAS HEIMANN, M.D., New York, NY.

ADRIAN J. GREENSTEIN, M.D., F.A.C.G., New York, NY., and

ARTHUR H. AUFSES, JR., M.D., F.A.C.G., New York, NY.

3:25 P.M.

Discussion.

3:30 P.M.

Coffee break and recess to visit the technical and scientific exhibits.

4:00 P.M.

32. Cimetidine Serum and CSF Levels in Patients with Mental Confusion.

JEROME J. SCHENTAG, Pharm.D., Buffalo, NY. (By invitation)

FRANK CERRA, M.D., Buffalo, NY. (By invitation), and

HAROLD BERNHARD, M.D., F.A.C.G., Buffalo, NY.

4:10 P.M.

Discussion.

4:15 P.M.

33. Circumscribed Atrophic Gastritis: Endoscopic and Histologic Correlation.

HOOSHANG MESHKINPOUR, M.D., Orange, CA. (By invitation)

ROBERT A. ORLANDO, M.D., Orange, CA. (By invitation)

JUAN F. ARGUELLO, M.D., Orange, CA. (By invitation), and

MICHAEL P. DEMICCO, M.D., F.A.C.G., Anaheim, CA.

4:25 P.M.

34. Endoscopic Recognition of Auto-Immune Gastritis.

ALBERT C. SVOBODA, JR., M.D., F.A.C.G., Santa Barbara, CA.

4:30 P.M.

Discussion of papers 33 and 34.

4:35 P.M.

35. Evaluation of Ultrasonically Powered Instruments on the Dog Viscera and in the Clinical Setting.

W. J. B. HODGSON, M.D., F.A.C.G., Bronx, NY.

P. K. PODDAR, M.D., Bronx, NY. (By invitation)

E. J. MENCER, M.D., Bronx, NY. (By invitation)

J. WILLIAMS, M.D., Bronx, NY. (By invitation)

M. DREW, M.D., Bronx, NY. (By invitation), and

A. J. MCELHINNEY, M.D., Bronx, NY. (By invitation).

4:45 P.M.

36. Complications of Diverticulitis and Their Management.

MALCOLM C. VEIDENHEIMER, M.D., F.A.C.G., Boston, MA.

4:55 P.M.

Discussion of papers 35 and 36.

7:00 P.M.

ANNUAL BANQUET—Salons D, E.

FIFTH SESSION

WEDNESDAY MORNING,

27 SEPTEMBER 1978

JEROME D. WAYE, M.D., F.A.C.G., New York, NY., Trustee and Chairman, Program Committee, American College of Gastroenterology, presiding.

9:00 A.M.

37. Medical and/or Surgical Treatment of the Amebic Liver Abscess.

DANIEL CUTLER G., M.D., F.A.C.G., Mexico City, Mexico

MIGUEL ANGEL ROJAS, M.D., Mexico City, Mexico (By invitation), and

MARTHA PANIAGUA, M.D., Mexico City, Mexico (By invitation).

9:10 A.M.

Discussion.

9:15 A.M.

38. Cryptogenic Hepatic Abscess in Two Uncompromised Children.

ELIZABETH HARRINGTON, M.D., New York, NY. (By invitation), and

MICHAEL A. BLEICHER, M.D., F.A.C.G., New York, NY.

9:25 A.M.

Discussion.

9:30 A.M.

39. Primary Biliary Cirrhosis: Natural History in the 1970's.

ANTHONY S. TORNAY, JR., M.D., F.A.C.G., Boston, MA., and

FREDERICK F. WHITCOMB, JR., M.D., F.A.C.G., Boston, MA.

9:40 A.M.

Discussion.

9:45 A.M.

40. Does Hyperamylasemia in the Drunken Alcoholic Signify Pancreatitis?

J. EDWARD BERK, M.D., F.A.C.G., Orange, CA.

LOUIS FRIDHANDLER, Ph.D., Orange, CA. (By invitation), and

SIDNEY WEBB, M.D., Orange, CA. (By invitation).

9:55 A.M.

Discussion.

10:00 A.M.

41. Cost Containment in Gastroenterology.

ABRAHAM J. KAUVAR, M.D., F.A.C.G., Denver, CO.

10:30 A.M.

Coffee break and recess to visit the technical and scientific exhibits.

11:00 A.M.

42. Keep Warm Stools Cold! Current Concepts in Parasitology.

C. RAY RATLIFF, Ph.D., F.A.C.G., Nashville, TN.

11:10 A.M.

Discussion.

11:15 A.M.

43. Esophageal Disease as a Cause of the Anginal Syndrome in Patients with Normal Coronary Angiograms.

PHILIP GROSSMAN, M.D., Miami, FL. (By invitation)

HARVEY G. KEMP, JR., M.D., New York, NY. (By invitation), and

NORTON S. ROSENSWEIG, M.D., Scarsdale, NY. (By invitation).

11:25 A.M.

Discussion.

11:30 A.M.

44. Randomized Control Trials (RCT) in the Surgical Therapy of Duodenal Ulcer.

EVERETT P. SHARECK, JR., M.D., Los Angeles, CA. (By invitation)

THOMAS C. CHALMERS, M.D., F.A.C.G. (Hon.), New York, NY.

HARRY SMITH, JR., Ph.D., New York, NY. (By invitation), and

BERNARD SILVERMAN, B.A., New York, NY. (By invitation).

11:45 A.M.

STUART DISTINGUISHED LECTURE OF THE AMERICAN COLLEGE OF GASTROENTEROLOGY

45. Alcohol and the Liver: Progress Through 1978.

CHARLES S. LIEBER, M.D., F.A.C.G., Bronx, NY.

SIXTH SESSION

WEDNESDAY AFTERNOON,

27 SEPTEMBER 1978

JOHN T. GALAMBOS, M.D., F.A.C.G., Atlanta, GA., Secretary-General, American College of Gastroenterology, presiding.

2:00 P.M.

46. PANEL ON DIARRHEA

Moderator

FRED KERN, JR., M.D., Denver, CO. (By invitation).

Participants

MARGOT SHINER, M.D., Harrow, U.K. (By invitation), and

WILLIAM C. SLOAN, M.D., F.A.C.G., Livingston, NJ.

3:00 P.M.

Question and Answer Period.

3:30 P.M.

Coffee break and recess to visit the technical and scientific exhibits.

4:00 P.M.

47. Endoscopic Sphincteroplasty: Can This Actually Be Accomplished Without Surgery?

JEROME H. SIEGEL, M.D., F.A.C.G., New York, NY.

4:10 P.M.

48. Ampullary Stenosis: Clinical Presentation, Diagnosis and Management.

JEFFREY B. RASKIN, M.D., Miami, FL. (By invitation)

EUGENE KAFKA, M.D., Miami, FL. (By invitation), and

JOE LEVI, M.D., Miami, FL. (By invitation).

4:20 P.M.

Discussion of papers 47 and 48.

4:30 P.M.

49. Absorption of Contrast After Endoscopic Retrograde Cholangiopancreatography (ERCP).

ROBERT A. SABLE, M.D., New York, NY. (By invitation)

JEROME H. SIEGEL, M.D., F.A.C.C., New York, NY.

RICKEY HO, M.D., New York, NY. (By invitation), and

WILLIAM S. ROSENTHAL, M.D., F.A.C.C., New York, NY.

4:40 P.M.

Discussion.

4:45 P.M.

50. Pancreatic Carcinoma: A Clinical Review and Schema for Evaluating Patients.

LEONARD A. WEINGARTEN, M.D., New York, NY

A. M. GELB, M.D., F.A.C.C., New York, NY., and

MURRY G. FISCHER, M.D., F.A.C.C., New York, NY.

4:55 P.M.

Discussion.

COURSE IN POSTGRADUATE GASTROENTEROLOGY

FIRST SESSION

THURSDAY MORNING,

28 SEPTEMBER 1978

Attendance at the Postgraduate Course is limited to those who have registered and paid the matriculation fee.

RICHARD G. FARMER, M.D., F.A.C.G., Cleveland, OH, President, American College of Gastroenterology, presiding.

9:00 A.M.

Welcome—DR. FARMER.

9:05 A.M.

AUXILIARY LECTURE

1. Contribution of Electron Microscopy to Our Knowledge of Small Intestinal Disease.

MARGOT SHINER, M.D., Harrow, U.K.

9:35 A.M.

PANEL ON THE SMALL INTESTINE

Moderator

JAMES W. MANIER, M.D., F.A.C.G., Marshfield, WI.

Paritcipants

2. Intestinal Malassimilation: Clinical Findings and Classification of Causes.

JAMES W. MANIER, M.D., F.A.C.G., Marshfield, WI.

3. Laboratory Diagnosis of Malabsorption.

FRED KERN, JR., M.D., Denver, CO.

4. Radiologic Diagnosis of Malabsorption.

RICHARD H. MARSHAK, M.D., F.A.C.G., New York, NY.

10:20 A.M.

Panel Discussion—Question and Answer Period.

11:00 A.M.

Coffee break.

11:20 A.M.

PANEL ON PANCREATITIS AND ITS CONSEQUENCES

Moderator

J. EDWARD BERK, M.D., F.A.C.G., Orange, CA.

Participants

5. Pancreatitis—Medical Aspects.

IRWIN J. PINCUS, M.D., F.A.C.G., Beverly Hills, CA.

6. Pancreatitis and Its Surgical Consequences.

DAVID A. DREILING, M.D., F.A.C.G., New York, NY.

12:10 P.M.

Question and Answer Period.

12:30 P.M.

LUNCHEON—Salon E.

SECOND SESSION

THURSDAY AFTERNOON,

28 SEPTEMBER 1978

Attendance at the Postgraduate Course is limited to those who have registered and paid the matriculation fee.

2:00 P.M.

PANEL ON ACID-PEPTIC DISEASE

Moderator

DAVID C. H. SUN, M.D., F.A.C.G., Phoenix, AZ.

Participants

7. Esophagitis—Its Occurrence and Complications.

GORDON MCHARDY, M.D., New Orleans, LA.

8. Management of Acid-Peptic Disease—Medical Update.

BASIL I. HIRSCHOWITZ, M.D., F.A.C.G., Birmingham, AL.

9. Management of Acid-Peptic Disease—Surgical Update.

GILBERT HERMANN, M.D., Denver, CO.

3:15 P.M.

Question and Answer Period.

3:35 P.M.

Coffee break.

3:50 P.M.

SPECIAL LECTURE

10. Gastrointestinal Hormones: Current Status in Normal and Abnormal States.

WILLIAM Y. CHEY, M.D., Rochester, NY.

4:30 P.M.

DR. HENRY BAKER LECTURE

11. Surgery, Enzyme Kinetics and a Way of Life.

JOHN T. GALAMBOS, M.D., F.A.C.G., Atlanta, GA.

5:00 P.M.

12. Round Tables—Meet the Professor, Small Group Discussions.

1. Alcoholic Liver Disease.

JOHN T. GALAMBOS, M.D., F.A.C.G., Atlanta, GA.

2. Endoscopy.

HENRY COLCHER, M.D., F.A.C.G., Birmingham, AL.

ANGELO E. DAGRADI, M.D., F.A.C.G., Long Beach, CA.

3. Esophagus.

GORDON MCHARDY, M.D., New Orleans, LA.

4. Gallbladder—Acalculous and Calculous.

FRANZ GOLDSTEIN, M.D., F.A.C.G., Philadelphia, PA.

5. Gastrointestinal Hormones.

WILLIAM Y. CHEY, M.D., Rochester, NY.

6. Hepatitis.

GARY L. GITNICK, M.D., Encino, CA.

7. Inflammatory Bowel Disease.

F. WARREN NUGENT, M.D., F.A.C.G., Boston, MA.

8. Malabsorption.

JAMES W. MANIER, M.D., F.A.C.G., Marshfield, WI.

9. Pancreatitis.

J. EDWARD BERK, M.D., F.A.C.G., Orange, CA.

10. Peptic Ulcer.

BASIL I. HIRSCHOWITZ, M.D., F.A.C.G., Birmingham, AL.

DAVID C. H. SUN, M.D., F.A.C.G., Phoenix, AZ.

THIRD SESSION

FRIDAY MORNING,

29 SEPTEMBER 1978

Attendance at the Postgraduate Course is limited to those who have registered and paid the matriculation fee.

9:00 A.M.

PANEL ON COLONIC DISEASES

Moderator

RICHARD G. FARMER, M.D., F.A.C.G., Cleveland, OH.

Participants

13. Diverticular Disease of the Colon.

F. WARREN NUGENT, M.D., F.A.C.G., Boston, MA.

14. Problems in Inflammatory Bowel Disease.

RICHARD G. FARMER, M.D., F.A.C.G., Cleveland, OH.

15. Malignant Potential in Inflammatory Bowel Disease.

F. WARREN NUGENT, M.D., F.A.C.G., Boston, MA.

16. Medical Treatment of Inflammatory Bowel Disease.

FRANZ GOLDSTEIN, M.D., F.A.C.G., Philadelphia, PA.

10:25 A.M.

Question and Answer Period.

10:45 A.M.

Coffee break.

11:00 A.M.

PANEL ON POLYP CANCER OF THE COLON

17. Early Detection of Colorectal Tumors with Flexible Sigmoidoscopy and Total Colonoscopy.

HENRY COLCHER, M.D., F.A.C.G., Birmingham, AL.

18. Practical Approaches to Screening and Early Diagnosis of Colon Cancer.

SIDNEY J. WINAWER, M.D., F.A.C.G., New York, NY.

11:35 A.M.

Question and Answer Period.

11:50 A.M.

SPECIAL LECTURE

19. Bile Acid Metabolism and Medical Dissolution of Gallstones.

FRED KERN, JR., M.D., Denver, CO.

12:30 P.M.

LUNCHEON—Salon E.

FOURTH SESSION

FRIDAY AFTERNOON,

29 SEPTEMBER 1978

Attendance at the Postgraduate Course is limited to those who have registered and paid the matriculation fee.

2:00 P.M.

PANEL ON ACUTE VIRAL HEPATITIS

Moderator

JOHN T. GALAMBOS, M.D., F.A.C.G., Atlanta, GA.

Participants

20. Alcoholic Hepatitis—Update.

JOHN T. GALAMBOS, M.D., F.A.C.G., Atlanta, GA.

21. Serologic Tests and Their Clinical Value.

GARY L. GITNICK, M.D., Encino, CA.

22. Prophylaxis—Hyperimmune Globulin vs. Commercial Globulin.

JOHN T. GALAMBOS, M.D., F.A.C.G., Atlanta, GA.

23. Controversy on Isolation of the Patient.

GARY L. GITNICK, M.D., Encino, CA.

24. Fulminant Hepatitis.

ALLAN G. REDEKER, M.D., Downey, CA.

3:15 P.M.

Question and Anwer Period.

3:30 P.M.

Coffee break.

3:50 P.M.

PANEL ON CHRONIC HEPATITIS

25. Immunological Mechanism.

JOHN T. GALAMBOS, M.D., F.A.C.G., Atlanta, GA.

26. Clinical Management of Chronic Hepatitis.

ALLAN G. REDEKER, M.D., Downey, CA.

4:40 P.M.

Question and Answer Period.

FIFTH SESSION

SATURDAY MORNING,

30 SEPTEMBER 1978

Attendance at the Postgraduate Course is limited to those who have registered and paid the matriculation fee.

9:00 A.M.

PANEL ON ENDOSCOPY

Moderator

BENJAMIN H. SULLIVAN, JR., M.D., Cleveland, OH.

Participants

27. Upper Gastrointestinal Endoscopy.

BENJAMIN H. SULLIVAN, JR., M.D., Cleveland, OH.

28. Endoscopic Cholangiography and Pancreatography, Endoscopic Sphincterotomy.

JACK A. VENNES, M.D., Minneapolis, MN.

29. Laparoscopy.

CHARLES J. LIGHTDALE, M.D., F.A.C.G., New York, NY.

30. Colonoscopy.

HENRY COLCHER, M.D., F.A.C.G., Birmingham, AL.

11:15 A.M.

Coffee break.

11:30 A.M.

Question and Answer Period.

12:45 P.M.

LUNCHEON—Salon E.

SCIENTIFIC EXHIBITS

Booth A

Primary Repair and Exteriorization of Colon Injuries.

SISTER MARY ANN LOU, M.D., F.A.C.G., Los Angeles, CA.

This exhibit demonstrates that primary repair and exteriorization is the safest most economical way of managing most penetrating colon injuries. There is a detailed illustration of technics of operative repair, exteriorization, and delayed interiorization of the colonic wound, with emphasis on avoidance of pitfalls such as infection, herniation, and obstruction at the site of injury.

Of 20 patients thus treated, 14 were successfully interiorized at 10-12 days, thereby avoiding colostomy. Six colon wounds that leaked at the repair site were converted to loop colostomies. This approach combines the safety of exteriorization with the low morbidity and economy of primary repair.

Booth B

Flexible Pansigmoidoscopy.

JAMES W. MANIER, M.D., F.A.C.G., Marshfield, WI.

Previous work has shown flexible pansigmoidoscopy to be easily done, with little expenditure of time, excellent patient acceptance and a high rate of discovery of additional lesions beyond rigid scope range. This exhibit shows that expanding the length of the scope from 65 to 105 cm. increased the depth of insertion from 58.5 to 70.2 cm. at a cost of 2.4 minutes with the pick up of one additional lesion. A comparison of findings in routine versus symptomatic patients showed no difference. A comparison of the ability of a resident physician and two staff physicians to learn to use the scope revealed no difference in depth of insertion but a longer examination time and more patient pain in the resident's patients. We conclude that the 65 cm. scope is an advance over the rigid sigmoidoscope, should be used in routine examinations, and can be quickly and easily learned by the novice.

Booth C

Flexible Fiberoptic Colonoscopy in the Total Management of the Patient with Colorectal Neoplasia.

GERALD MARKS, M.D. and BENJAMIN HASKELL, M.D., Philadelphia, PA.

The exhibit describes a totally comprehensive scheme for the application of the flexible fiberoptic colonoscope in the management of the patient with, or at high-risk of having colorectal neoplasia. The scheme should promote: a. ready diagnosis and destruction of premalignant and early malignant lesions, b. improvement of thorough and safe surgical management and c. enchancement of protective surveillance of patients identified as high-risk. The application of flexible fiberoptic colonoscopy is directed to patients in three categories: 1. polypoid disease, 2. cancer and 3. high-risk status.

Polypoid disease is addressed in terms of diagnosis, polypectomy, technic, judgmental aspects and surveillance. *Cancer* is considered in terms of diagnosis, radiographic confirmation, preoperative evaluation, anastomotic inspection and surveillance. *High-risk status* patients are identified as those with prior carcinoma of the colon, prior history of colonic polyps, strong familial history, multiple polyposis states, chronic ulcerative colitis, granulomatous colitis, radiation colitis, breast-uterine cancer, ureterosigmoidostomy and cancer family syndrome.

The exhibit contains a latex model of the colon set up for examination with a flexible fiberoptic sigmoidoscope. Television transmission from the scope via a Circon camera to an overhead monitor permits a number of viewers to see the various cancers and polyps contained within the colon model and visualized by the examiner. Centrally located graphics describe the polyp/cancer sequence as well as two maps of the colon indicating the changing site distribution of colorectal cancer at the Thomas Jefferson University Hospital through the periods covering 1939-1953 and 1957-1977. The changing site distribution underscores the diminishing effectiveness of digital rectal and rigid sigmodoscopic examinations.

Booth D

Enzyme Replacement Therapy in Pancreatic Insufficiency.

GEORGE L. BLACKBURN, M.D., Ph.D., DAVID VALERIO, M.D. and ERIC WHYTE, B.A., Boston, MA.

We have studied the efficacy of delivering exocrine pancreatic enzyme in the form of encapsulated, enteric-coated micropsheres to patients with severe pancreatic insufficiency. Delivering the pancrelipase in this form is intended to insure the rapid passage of the microspheres through the pylorus and release of the enzyme in the duodenum while the ingested food is present.

The study consisted of fecal fat balance studies on 23 patients, comparing the microspheres to placebo in one group and to several commercial pancreatic enzyme replacements in another group. The microsphere preparation showed improved fat utilization ($p < 0.05$) and stool frequency ($p < 0.01$) over existing preparations. Long-term studies show significant weight gain among study patients.

The exhibit presents the problems with pancreatic enzyme replacement, the outline of this study, results of both study groups in both short-term and long-term, and our conclusions.

Booth E

Transverse Taeniamyotomy.

W. JOHN B. HODGSON, M.D., F.A.C.G. and A. JAMES MCELHINNEY, M.D., Bronx, NY.

Tansverse taeniamyotomy is an anatomical, physiological and conservative method of correction of the abnormal physiology of colonic muscle present in diverticular disease. In this exhibit the rationale, technic and results in 34 patients are demonstrated.

Transverse taeniamyotomy (TVM) is performed by making multiple transverse incisions at intervals in the two antimesenteric *taeniae coli* of the affected shortened, plicated and narrowed colon of diverticular disease. These changes were reversed and improvement demonstrated at six weeks postoperatively was maintained throughout the two-year follow-up. TVM has also been successfully used in four cases of diverticulitis and in combination with resection in ten cases.

TVM allows the surgeon to employ a graded response to increasingly severe pathological changes. TVM has been effective in localized diverticulitis and chronic diverticular disease. It has been used in moderately severe diverticulitis in combination with resection and allows staged procedures to be reserved for perforations.

Booth F

Polyp-Cancer Sequence of the Colon.

JACOB WEINSTEIN, M.D., F.A.C.G., Washington, DC.

A 20-year study of 200 patients with small asymptomatic polyps was carried out to throw light on the polyp-cancer sequence.

In that time, of those with atypical adenomas, 20% developed other adenomas and 6% cancer. In those with atypical polyps, 50% developed other polyps and 20% cancer.

Patients with atypical polyps represent a greater susceptibility to the etiologic agents causing polyps and cancer. This is the crux of the polyps-cancer sequence.

The removal of all polyps by sigmoidoscopy and colonoscopy will practically prevent the development of cancer of the colon.

Booth G

Living Healthy—ADDS as Physician Aid.

AMERICAN DIGESTIVE DISEASE SOCIETY, New York, NY.

Concentrating on the problems of dealing with patient management after the treatment has been prescribed. Educational materials designed for the patient's interest in digestive health, nutrition, stress and tension, psychology and physiology.

ADDS helps make this kind of patient care cost-efficient for the physician. The booth shows how.

Booth H

Vasodilatation in the Layers of the Gastrointestinal Tract Caused by Intravenous Infusion of Papavarine and Pentagastrin.

MARCUS DUGAS, Ph.D. and RICHARD L. WECHSLER, M.D., F.A.C.G., Pittsburgh, PA.

Papavarine has been shown to dilate large mesenteric vessels. However, its use in ischemic bowel disease is rare. Therefore, we studied its effects on the circulation through the small vessels of the three layers of the entire gastrointestinal tract.

Booth K

Therapeutic Applications of Catheter Colangiography.

ERNEST J. RING, M.D., JUAN A. OLEAGA, M.D. and DAVID FREIMAN, M.D., Philadelphia, PA.

Sixteen patients with obstructive jaundice underwent percutaneous transhepatic cholangiography at the Hospital of the University of Pennsylvania. In 15 cases the biliary tree was successfully catheter-

ized using an 18 gauge needle within a thin-walled polyethylene sheath. The sheath was replaced by an angiographic catheter using the Seldinger technic. In two cases an external drainage was established. In the remaining 13 cases the catheter could be advanced across the obstruction and replaced with a larger catheter. Sideholes placed in the larger catheter above and below the obstruction permitted internal drainage through the catheter into the duodenum for long-term stenting of bile duct injuries.

Booth L

National Commission on Digestive Diseases.

NATIONAL COMMISSION ON DIGESTIVE DISEASES, Bethesda, MD.

This exhibit will present an update on the Congressionally mandated National Commission on Digestive Diseases. Information will be presented about the mission, goals, activities and public hearings of the Commission.

The Commission is concerned with a wide range of problems, including determination of the incidence, duration, mortality, and morbidity rates, and social and economic impact of digestive diseases. Other duties involve an evaluation of public and private resources for the diagnosis, prevention, treatment of, and research in such diseases, and the identification of existing programs which are effective in improving the management of digestive diseases.

Booth M

Your Patient is Not Alone.

NATIONAL FOUNDATION FOR ILEITIS AND COLITIS, INC., New York, NY.

The National Foundation for Ileitis and Colitis, Inc. is devoted to a three-part program for conquering inflammatory bowel disease, shown photographically in this display. First, to sponsor basic and clinical research into the cause, treatments and cure for these diseases. Second, to inform the lay public, particularly patients and their families, about the current knowledge in this field. And third, to assist the clinician by providing updated information on diagnostic and treatment technics. The Foundation, comprised of physician and lay members, is the largest nonprofit agency in the digestive disease field.

Booth N

Percutaneous Transhepatic Insertion of a Permanent Internal Prosthesis in the Biliary Tree. A New Transhepatic Method for the Relief of Obstructive Jaundice.

RAUL PEREIRAS, M.D., Miami, FL.

Decompression of the biliary tree is essential for benign or malignant biliary tract obstruction. Palliative surgical drainage procedures include multiple by-pass procedures, the operative mortality of which has been reported to be between 23 and 33%, rising to 59% with extensive metastic disease. Percutaneous external transhepatic biliary drainage technics have also been devised as an alternative to surgery. We have devised a new nonsurgical method of relieving the obstruction by dilating the lesion and then placing a teflon prosthesis, bridging the narrowed segment. The potential benefits of this relatively simple procedure and our clinical experience with 17 patients will be discussed.

TECHNICAL EXHIBITORS

(Those attending the Convention sessions are urged to take advantage of the time in between the presentations of papers and sessions, to visit the technical exhibits and become acquainted with the many new products and new equipment on display.)

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Representatives look forward to the opportunity to discuss their products and services with you.

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Marion Laboratories, Inc. **Booth 26**
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Watertown, MA **Booth 28**

Their line of Soft Steerable Catheters; featuring a new Steerable Suction Biopsy Device, and a system for rapid G. I. Intubation for decompression or sampling will be shown. Also on display will be the Burhenne System for Non-Operative Biliary Stone Removal, and Accessories for Endoscopic Procedures.

Merrell-National Laboratories **Booth 23**
Cincinnati, OH

Bentyl®; dicyclomine hydrochloride USP; Cantil®, mepenzolate bromide NF; Cephulac®, lactulose, Syrup; Delcid® High Capacity Antacid; Kolantyl®.

Narco Bio-Systems, Inc. **Booth 19**
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Bio-Systems Manometric System.

Olympus Corporation of America **Booths 1, 2, 3**
New Hyde Park, NY

Flexible fiberoptic endoscopes; Ancillary equipment; accessories: biopsy forceps, snares, automatic camera system.

Ortho Pharmaceutical Corporation **Booth 18**
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Pharmacia Laboratories **Booth 11**
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Azulfidine®; Rectoid®; Silon® Spray.

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Proctofoam-HC; Phazyme-95; Trichotine; Trichotine-D; Proctofoam N/S; Cortifoam; Kwell; R & C Spray; Phazyme.

William H. Rorer, Inc. **Booths 9, 10**
Fort Washington, PA

Maalox Plus; Maalox; Ascriptin; Ascriptin A/D.

Rowell Laboratories, Inc. **Booth 6**
Baudette, MN

Cortenema 100 mg., Hydrocortisone; Orasone, Prednisone USP 20 & 50; Proctocort.

W. B. Saunders Company **Booth 30**
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Medical Books.

Searle Laboratories **Booth 16**
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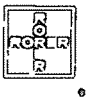
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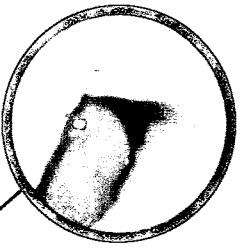
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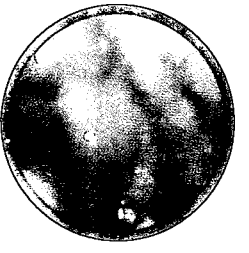
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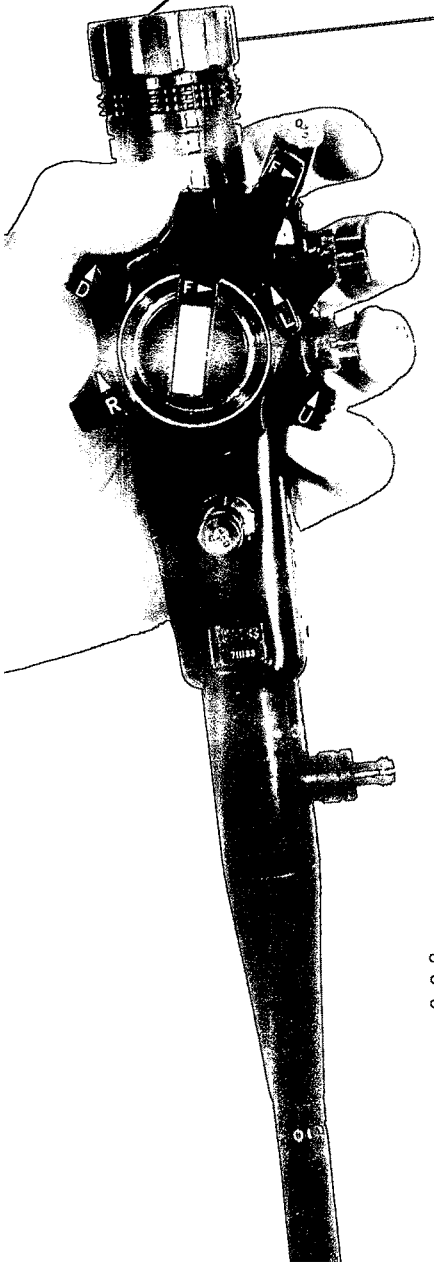


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21, 22, 23, 24 October 1979

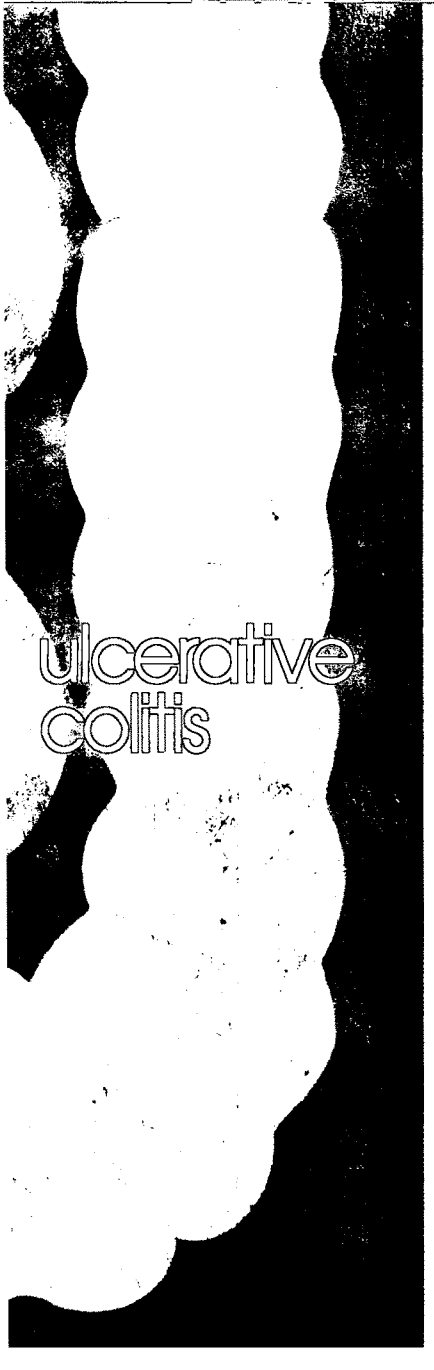
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††Please see Prescribing Information on next page.

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Continued effectiveness of IMODIUM in 18 patients after 6 to 18 months[1]

Median number of stools remained constant: **2/day**

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Median daily dosage remained constant: **4 capsules/day**

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"Due to its efficacy, rapid onset and long duration of action, lack of long-term drug tolerance, and simple individualized dosage regimen, [IMODIUM] is likely to become one of the commonly used agents for the treatment of chronic diarrhea."

1 Galambos, JT et al Gastroenterology 70 1026, June 1976.

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Brief Summary: Before prescribing, please consult complete prescribing information, a summary of which follows.

DESCRIPTION: IMODIUM (loperamide hydrochloride), 4-(*p*-chlorophenyl)-4-hydroxy-N,N-dimethyl-α,α-diphenyl-1-piperidinebutyramide monohydrochloride, is a synthetic antidiarrheal for oral use

IMODIUM capsules are classified as a Schedule V controlled substance by federal law (see: Overdosage Section)

CONTRAINDICATIONS: IMODIUM is contraindicated in patients with known hypersensitivity to the drug and in those in whom constipation must be avoided

WARNINGS: Antiperistaltic agents should not be used in acute diarrhea associated with organisms that penetrate the intestinal mucosa, e.g., toxigenic *E. coli*, *Salmonella*, *Shigella*, and in pseudomembranous colitis associated with broad-spectrum antibiotics

Fluid and electrolyte depletion may occur in patients who have diarrhea. The use of IMODIUM does not preclude the administration of appropriate fluid and electrolyte therapy. In some patients with acute ulcerative colitis, agents which inhibit intestinal motility or delay intestinal transit time have been reported to induce toxic megacolon. IMODIUM therapy should be discontinued promptly if abdominal distention occurs or if other untoward symptoms develop in patients with acute ulcerative colitis.

PRECAUTIONS: In acute diarrhea, if clinical improvement is not observed in 48 hours, the administration of IMODIUM should be discontinued.

Abuse and Dependence. Physical dependence to IMODIUM in humans has not been observed. However, studies in monkeys demonstrated that loperamide hydrochloride at high doses produced symptoms of physical dependence of the morphine type.

Carcinogenesis. In an 18-month rat study with doses up to 133 times the maximum human dose (on a mg/kg basis) there was no evidence of carcinogenesis.

Pregnancy. Safe use of IMODIUM during pregnancy has not been established. Reproduction studies performed in rats and rabbits with dosage levels up to 30 times the human therapeutic dose did not demonstrate evidence of impaired fertility or harm to the offspring due to IMODIUM. Higher doses impaired maternal and neonate survival, but no dose level up to 30 times the human dose demonstrated teratogenicity. Such experience cannot exclude the possibility of damage to the fetus. IMODIUM should be used in pregnant women only when clearly needed.

Nursing Mothers. It is not known whether IMODIUM is excreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

Pediatric Use. Safety and effectiveness in children have not been established. Therefore, use of IMODIUM is not recommended in the pediatric age group (under the age of 12). In case of accidental ingestion of IMODIUM by children, see Overdosage Section for suggested treatment.

ADVERSE REACTIONS: The adverse effects reported during clinical investigations of IMODIUM are difficult to distinguish from symptoms associated with the diarrheal syndrome. Adverse experiences recorded during clinical studies with IMODIUM were generally of a minor and self-limiting nature. They were more commonly observed during the treatment of chronic diarrhea.

The following patient complaints have been reported: Abdominal pain, distention or discomfort; constipation; drowsiness or dizziness; dry mouth; nausea and vomiting; tiredness.

Hypersensitivity reactions (including skin rash) however, have been reported with IMODIUM use.

IMODIUM Capsule shells contain tartrazine. Allergic reactions have been reported with the ingestion of this dye in some patients.

OVERDOSAGE: Animal pharmacological and toxicological data indicate that overdosage in man may result in constipation, CNS depression, and gastrointestinal irritation. In clinical trials an adult who took three 20 mg doses within a 24-hour period was nauseated after the second dose and vomited after the third dose. If vomiting has occurred spontaneously, a slurry of 100 gm of activated charcoal should be administered orally as soon as fluids can be retained.

If vomiting has not occurred, gastric lavage should be performed followed by administration of 100 gm of the activated charcoal slurry through the gastric tube. In the event of overdosage, patients should be monitored for signs of CNS depression for at least 24 hours. If CNS depression is observed, naloxone may be administered. If responsive to naloxone, vital signs must be monitored carefully for recurrence of symptoms of drug overdose for at least 24 hours after the last dose of naloxone. In view of the prolonged action of loperamide and the short duration (one to three hours) of naloxone, the patient must be monitored closely and treated repeatedly with naloxone as indicated. Based on the fact that relatively little drug is excreted in urine, forced diuresis is not expected to be effective for IMODIUM overdosage.

HOW SUPPLIED: IMODIUM is available as 2 mg capsules of loperamide hydrochloride. The capsules have a light green body and a dark green cap, with "ORTHO 1000" imprinted on each segment. IMODIUM capsules are supplied in bottles of 100.

IMODIUM (loperamide hydrochloride) is an original product of Janssen Pharmaceutica, Belgium and co-developed by Ortho Pharmaceutical Corporation. U.S. Patent 3,714,159

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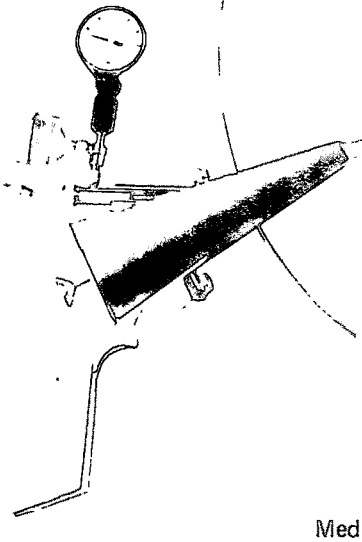
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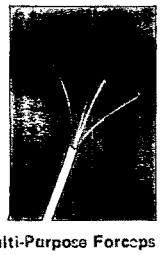


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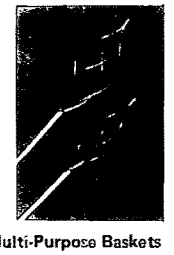
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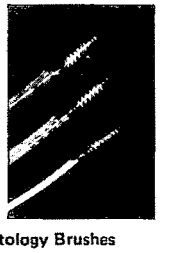
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Letters of transmittal which do not contain the above, signed by all the authors of the manuscript submitted, will necessitate delaying the review of the material.

Manuscripts must be typewritten on 8½ × 11 inch, white paper, double-spaced including references, legends, case reports and footnotes. Sufficient margins should be left at top, bottom and on the sides of each page.

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Each manuscript should begin with a short summary of not more than 150 words. The summary should contain the salient facts, i.e. purpose, results and conclusions. It will appear at the *beginning* of the article.

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The references should be typed double-spaced and abbreviations of journals should conform to those used in Index Medicus of the National Library of Medicine. The format is listed in the following examples:

References to an article with *3 or less authors:*

1. Robinson AS, Sommer DA, Levinson M: Transfiberscopic removal of esophageal polyps. Am J Gastroenterol 61:297-300, 1974.

References to an article with *more than 3 authors:*

2. Starzl TE, Lee IY, Porter KA, et al: The influence of portal blood upon lipid metabolism in normal and diabetic dogs and baboons. Surg Gynecol Obstet 140:381-388, 1975.

Reference to a book:

3. Reuter SR, Redman HC: Gastrointestinal Angiography. Second Edition. Philadelphia, W. B. Saunders Company, 1977.

Reference to an article in a book:

4. Ansel HJ: Normal Pancreatic Duct. *In:* Atlas of Endoscopic Retrograde Cholangiopancreatography. Edited by Stewart, ET, Vennes JA, Geenen JE. St. Louis, The C. V. Mosby Company, 1977, pp. 43-47.

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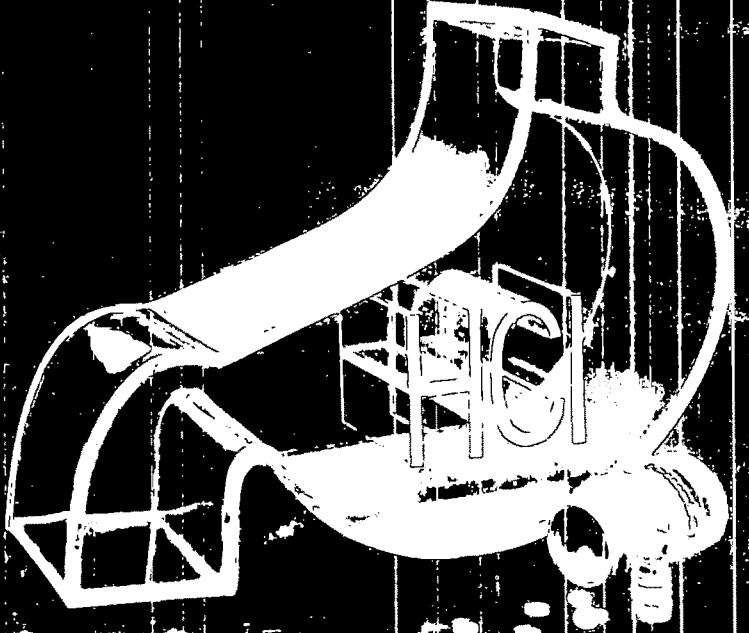
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Significant gastric acid suppression means effective duodenal ulcer therapy



Tagamet®

brand of cimetidine

Tablets, 300 mg. Injection, 300 mg./2 ml

The H_2 Receptor Antagonist

Working directly at the parietal cell, 'Tagamet' suppresses gastric acid secretion after meals and throughout the night, producing important patient benefits:

• rapid ulcer healing

• effective symptom relief, day and night

In *Duodenal Ulcer,* the recommended dosage is 300 mg. four times a day, with meals and at bedtime. Treatment periods should not exceed eight weeks.

While healing may occur during the first week or two, 'Tagamet' therapy should be continued for four to six weeks unless healing has been demonstrated endoscopically.

In *Pathological Hypersecretory Disorders,* the dosage is also 300 mg. four times a day, with meals and at bedtime. In some patients it may be necessary to administer 'Tagamet' 300 mg. doses more frequently (not to exceed 2400 mg. per day) and continue as long as clinically indicated.

Dosage should be reduced in patients with impaired renal function.

Concomitant antacids should be given as needed for relief of pain.

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

Indications: 'Tagamet' (brand of cimetidine) is indicated in the short-term (up to 8 weeks) treatment of duodenal ulcer; and in the treatment of pathological hypersecretory disorders (i.e., Zollinger-Ellison syndrome, systemic mastocytosis and multiple endocrine adenomas). Concomitant antacids should be given as needed for relief of pain. Studies to date do not provide evidence of the safety of cimetidine in uncomplicated duodenal ulcer beyond 8 weeks.

Contraindications: There are no known contraindications to the use of 'Tagamet'.

Precautions: In a 24-month toxicity study in rats at dose levels approximating 9 to 56 times the recommended human dose, benign Leydig cell tumors were seen. These were common in both the treated and control groups, and the incidence became significantly higher only in the aged rats receiving 'Tagamet'. Reproduction studies in animals have shown no evidence of impaired mating performance or fertility.

Lack of experience to date precludes recommending 'Tagamet' for use in pregnant patients, women of childbearing potential, nursing mothers or children under 16 unless anticipated benefits outweigh potential risks; generally, nursing should be discontinued in patients taking the drug.

Adverse Reactions: Diarrhea, muscular pain, dizziness, rash, mild gynecomastia. A few cases of neutropenia have been reported, but no causal relationship could be established. Small, regularly observed, reversible increases in plasma creatinine and some increases in serum transaminase have been reported.

How Supplied: Pale Green Tablets: 300 mg. tablets in bottles of 100 and Single Unit Packages of 100 (intended for institutional use only).

Injection: 300 mg./2 ml. in single-dose vials in packages of 10.

Date of issuance Sept. 1977

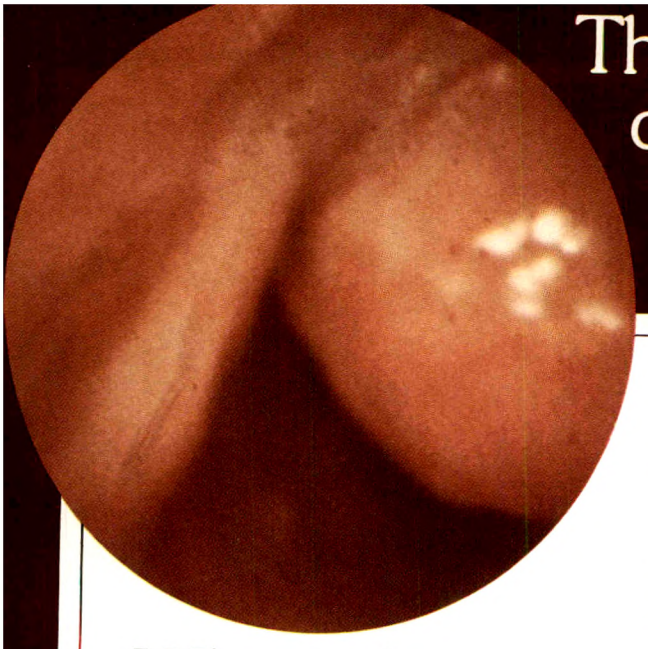
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The patient has dysphagia of 1½ years' duration.

Physical exam is unrevealing. X-ray studies are inconclusive.

What is the diagnosis?

Esophagoscopy resolves the question.

A 56-year-old man was seen because of increasingly severe dysphagia of one and a half years' duration. At the time of admission, the patient could take only liquids. Physical examination was unrevealing.

A filling defect of the midesophagus was observed by the radiologist. On several projections it appeared to be extrinsic, although an intrinsic lesion, such as leiomyoma, could not be excluded.

Esophagoscopy was performed, and a round submucosal tumor thought to be a *leiomyoma* was identified at the level of 28 cm from the incisor teeth. The patient refused surgical intervention.

Causes of dysphagia may include esophageal carcinoma, achalasia, lower esophageal ring or esophageal web, as well as benign neoplasm. Benign tumors are rare and when detected are usually only incidental findings. Such tumors may, however, become symptomatic upon reaching a large enough size. Such tumors are most often *leiomyomas*, which can partially obstruct the esophageal lumen. Characteristically, they develop central ulceration and hemorrhage.

Case discussion based on *The Clinical Significance of Esophagoscopy* by Bernard M. Schuman, M.D., one in a series of monographs made available by Roche Laboratories in fulfillment of its commitment to continuing education in gastroenterology. This case history illustrates the diagnostic use of endoscopy: it does not represent an indication for Librax therapy.

Endoscopy

–confirmatory or contradictory–

a valuable aid in the diagnosis of G.I. disorders

The development of highly specialized fiberoptic endoscopes has significantly enhanced the accuracy and efficiency of gastrointestinal diagnosis and treatment. Frequently, when both x-ray and laboratory tests have been repeatedly negative, endoscopy has uncovered an organic lesion.

Whether a G.I. condition is eventually confirmed as functional or organic, every patient should receive a thorough examination of his emotional profile and life stresses; such factors may give rise to the patient's symptomatic complaints or aggravate the symptoms of an organic disorder.

Librax®: a valuable aid in the treatment of irritable bowel syndrome*

The diagnosis of irritable bowel syndrome is based on the patient's symptoms and history, plus the exclusion of an organic disorder. In this condition, Librax has been found doubly valuable as an adjunct to reassurance and counseling because it relieves distressing symptoms of both emotional and somatic origin.

1 Only Librax provides the specific antianxiety action of Librium® (chlordiazepoxide HCl), in addition to the antisecretory-antispasmodic actions of Quarzan® (clidinium Br)—both original developments of Roche research.

2 Librax seldom impairs mental acuity or performance when given in proper dosage. However, as with all preparations containing CNS-acting agents, patients should be cautioned against hazardous occupations requiring complete mental alertness.

3 Flexibility of dosage helps meet varying requirements: 1 or 2 capsules three or four times daily, before meals and at bedtime.

4 The convenience and economy of a single Rx help sustain patient compliance, while providing relief of both emotional and somatic symptoms.

A distinctive antianxiety-antispasmodic agent

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Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium Br.

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*Librax has been evaluated as possibly effective for this indication. Please see brief summary of prescribing information on following page.

Librax®

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium Br.

Please consult complete prescribing information, a summary of which follows:

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows: "Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Physical and psychological dependence rarely reported on recommended doses, but use caution in administering Librium® (chlordiazepoxide HCl) to known addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions) reported following discontinuation of the drug.

Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.**

As with all anticholinergics, inhibition of lactation may occur.

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established.

Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.

Dosage: Individualize for maximum benefit. Usual maintenance dose is 1-2 capsules, 3-4 times/day, before meals and at bedtime. Geriatric patients—see Precautions.

How Supplied: Available in green capsules, each containing 5 mg chlordiazepoxide HCl (Librium®) and 2.5 mg clidinium Br (Quarzan®)—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 50, singly and in trays of 10.

ROCHE

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Manati, Puerto Rico 00701

MEETINGS OF INTEREST

44th Annual Convention, American College of Gastroenterology, Disneyland Hotel, Anaheim, CA, 22-24 October 1979.

Annual Course in Postgraduate Gastroenterology, American College of Gastroenterology, Disneyland Hotel, Anaheim, CA, 25-27 October 1979.

Portal Hypertension and Its Complications—Update. Postgraduate Course of the American Association for the Study of Liver Disease, Chicago, IL, 7-8 November 1978.

One Day of Gastroenterology, Postgraduate Course co-sponsored by the American College of Gastroenterology, the Southern Medical Association. Georgia World Congress Center, Atlanta, GA, 11 November 1978.

International Conference on Digestive Diseases, Postgraduate Course co-sponsored by the American College of Gastroenterology, the University of South Florida Medical School in Tampa and the Florida Hospital in Orlando. Dutch Inn, Lake Buena Vista, FL, 28-30 January 1979.


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Hydrocortisone Retention Enema

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☐ **An effective alternative to oral corticosteroids**—lessens risk of possible complications due to systemic absorption

☐ **Provides soothing, direct relief** from ulcerative colitis symptoms—effective medication in a vehicle providing coverage of inflamed colonic mucosa

☐ **Premeasured, prefilled, prelubricated, disposable**—for unit dose convenience, dosage accuracy, patient comfort

☐ **Supplied in a convenient, economical seven-pack**—design to meet your prescribing needs

☐ **From the leaders in chemotherapy of ulcerative colitis for over 30 years.**

See facing page for brief summary of prescribing information.

New from Pharmacia

THE MOST DIRECT ROUTE TO RELIEF IN ULCERATIVE COLITIS

RECTOID®

Hydrocortisone Retention Enema

INDICATIONS: Adjunctive therapy in the treatment of ulcerative colitis.
CONTRAINDICATIONS: Systemic fungal infections; during the immediate or early postoperative period following ileocolostomy.
WARNINGS: Prolonged use may cause systemic reactions. Do not delay needed surgery while awaiting response to medical treatment. Proper insertion of the enema tip is essential to prevent rectal wall damage. Increased dosages are indicated before, during and after unusually stressful situations. Signs of infection may be masked, and new infections may appear, along with decreased resistance and decreased ability to localize infection.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Adequate human reproduction studies have not been done with corticosteroids. In pregnancy, nursing mothers or women of childbearing potential, weigh the possible benefits of the drug against the possible hazards to the mother and the embryo or fetus. Observe infants born of mothers treated during pregnancy for signs of hypoadrenalism.

Elevation of blood pressure, salt and water retention and increased excretion of potassium, requiring dietary restrictions and supplementation, may occur. All corticosteroids increase calcium excretion. *Immunization procedures, especially against smallpox, should not be undertaken in patients receiving corticosteroids, because of the possible hazard of neurological complications and lack of antibody response.* Close observation and chemoprophylaxis are indicated in patients with latent tuberculosis or tuberculin reactivity.
PRECAUTIONS: Use with caution in cases of impending perforation, abscess or other pyogenic infection, fresh intestinal anastomoses, obstruction, extensive fistulas, and in the presence of active or latent peptic ulcer, diverticulitis, renal insufficiency, hypertension, osteoporosis, or myasthenia gravis. Surgical prognosis may be impaired by increased infection hazard. Administer larger dose of appropriate antibiotics if infection is suspected. Drug-induced secondary adrenocortical insufficiency, minimized by a gradual dosage reduction, may occur with prolonged therapy. This condition may persist for months after discontinuation of therapy; therefore, hormone therapy should be reinstituted during periods of stress. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently. Corticosteroids exhibit an enhanced effect in patients with hypothyroidism and cirrhosis and should be used cautiously in patients with ocular herpes simplex because of possible cornea perforation. Use the lowest possible dose to control the condition and institute a gradual dosage reduction as soon as possible.

Psychic derangement may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids. Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.
ADVERSE REACTIONS: Local pain or burning, rectal bleeding, and apparent exacerbations of the disease or sensitivity reactions may occur in rare instances. The following adverse reactions should be kept in mind whenever corticosteroids are given.
Fluid and Electrolyte Disturbances: Sodium retention; fluid retention; congestive heart failure in susceptible patients; potassium loss; hypokalemic alkalosis; hypertension. *Musculoskeletal:* Muscle weakness; steroid myopathy; loss of muscle mass; osteoporosis; vertebral compression fractures; aseptic necrosis of femoral and humeral heads; pathologic fracture of long bones. *Gastrointestinal:* Peptic ulcer with possible perforation and hemorrhage; pancreatitis; abdominal distention; ulcerative esophagitis. *Dermatologic:* Impaired wound healing; thin fragile skin; petechiae and ecchymoses; facial erythema; increased sweating; may suppress reactions to skin tests. *Neurological:* Convulsions; increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment; vertigo; headache. *Endocrine:* Menstrual irregularities; development of Cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirement for insulin or oral hypoglycemic agents in diabetics. *Ophthalmic:* Posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos. *Metabolic:* Negative nitrogen balance due to protein catabolism.
DOSAGE AND ADMINISTRATION: The usual course of therapy is one RECTOID enema nightly for 21 days.

Sigmoidoscopic examination and x-ray visualization are essential for adequate monitoring.
HOW SUPPLIED: Boxes of seven 60 ml (hydrocortisone 100 mg) disposable single dose bottles with lubricated rectal applicator tips.
IMPORTANT: See full prescribing information before administering RECTOID.

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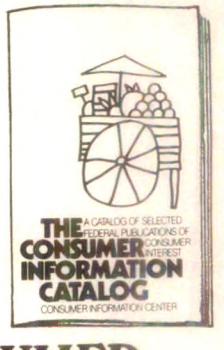
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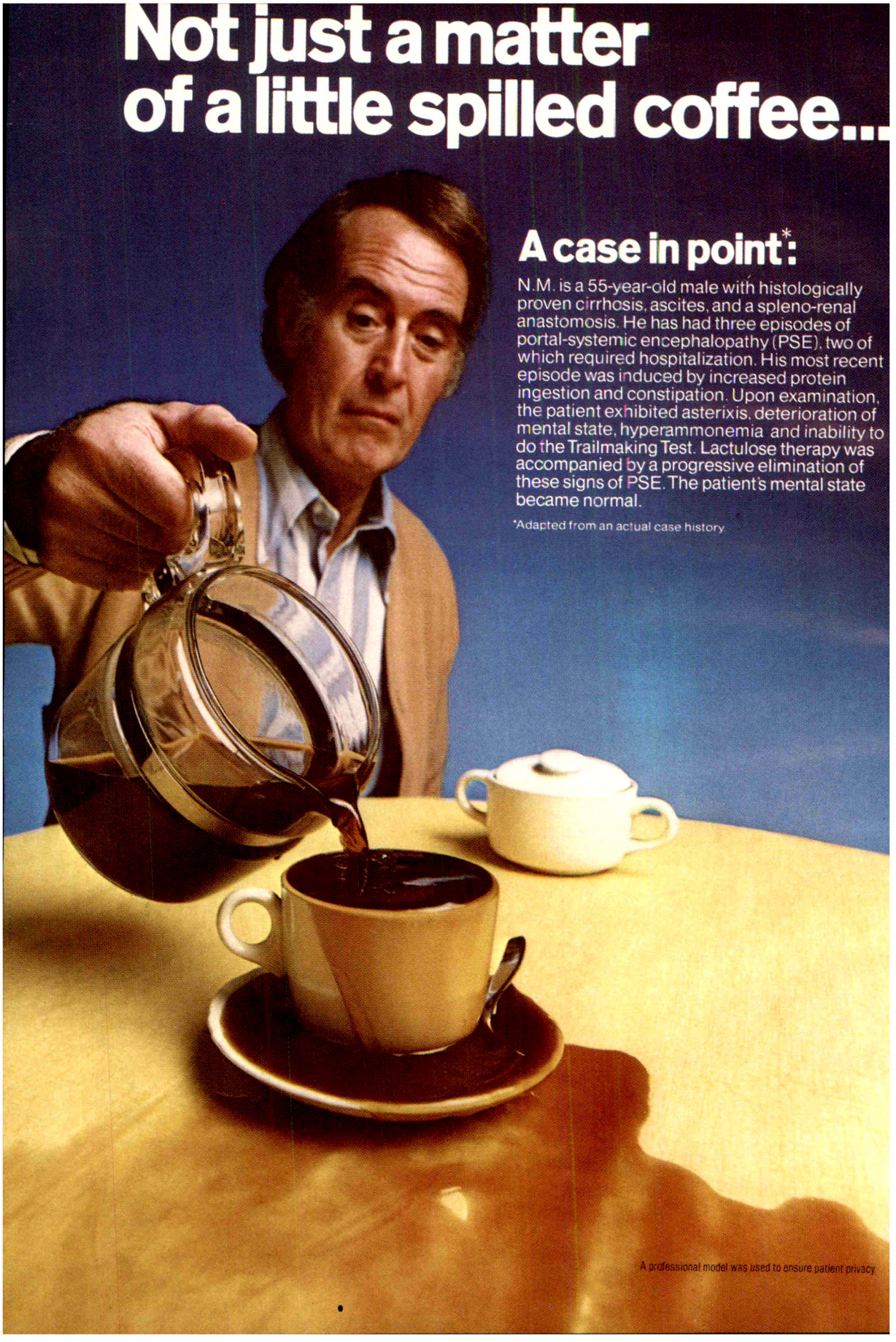


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Not just a matter of a little spilled coffee...



A case in point*:

N.M. is a 55-year-old male with histologically proven cirrhosis, ascites, and a spleno-renal anastomosis. He has had three episodes of portal-systemic encephalopathy (PSE), two of which required hospitalization. His most recent episode was induced by increased protein ingestion and constipation. Upon examination, the patient exhibited asterixis, deterioration of mental state, hyperammonemia and inability to do the Trailmaking Test. Lactulose therapy was accompanied by a progressive elimination of these signs of PSE. The patient's mental state became normal.

*Adapted from an actual case history

A professional model was used to ensure patient privacy

.this is portal-systemic encephalopathy (PSE)–

(Also called Hepatic Encephalopathy, pre-Hepatic Coma)

–a common complication of chronic liver disease.

Suspect PSE in every patient with cirrhosis.

Common early symptoms

- irritability
- euphoria
- lack of concern for others
- inappropriate behavior
- faraway look
- inversion of sleep pattern

Results of recent investigations of PSE

- Two-thirds of cirrhotic patients with portal hypertension who appeared mentally normal by conventional assessment revealed impairment of cerebral function on psychomotor testing. This dysfunction was in the same range as that in patients with brain damage after blunt trauma.[1]
- Alcoholic males with cirrhosis demonstrated a mental state significantly inferior to alcoholics without cirrhosis.[2]
- The majority of cirrhotic patients with portacaval shunts who appeared mentally normal had demonstrable psychomotor impairment.[3]

Treat PSE with Cephulac (lactulose) Syrup

- relieves PSE in 75% of episodes
- acts without serious adverse reactions
- lowers blood ammonia levels
- improves EEG and mental state
- permits more normal dietary protein intake
- provides an easy-to-manage means of long-term therapy

Cephulac®
(lactulose) Syrup

Each 15 ml. of syrup contains: 10 g. lactulose (and less than 2.2 g. galactose, less than 1.2 g. lactose, and 1.2 g. or less of other sugars)

for the prevention and treatment of PSE in your patients with chronic liver disease

Merrell

MERRELL-NATIONAL LABORATORIES
Division of Richardson-Merrell Inc
Cincinnati, Ohio 45215

Brief Summary

INDICATIONS: For the prevention and treatment of portal-systemic encephalopathy, including the stages of hepatic pre-coma and coma. Controlled studies have shown that lactulose syrup therapy reduces the blood ammonia levels by 25-50%; this is generally paralleled by an improvement in the patients' mental state and by an improvement in EEG patterns. The clinical response has been observed in about 75% of patients, which is at least as satisfactory as that resulting from neomycin therapy. An increase in patients' protein tolerance is also frequently observed with lactulose therapy. In the treatment of chronic portal-systemic encephalopathy, Cephulac has been given for over 2 years in controlled studies.

CONTRAINDICATIONS: Since Cephulac contains galactose (less than 2.2 g./15 ml.), it is contraindicated in patients who require a low galactose diet.

WARNINGS: *Use in Pregnancy:* Studies in laboratory animals have not revealed a teratogenic potential of lactulose. The safety of lactulose syrup during pregnancy and its effect on the mother or the fetus have not been evaluated in humans. The physician and patient should understand that the possibility that lactulose syrup might cause damage to the human fetus cannot be excluded. Lactulose syrup should not be given during pregnancy unless, in the opinion of the physician, the possible benefits outweigh the possible risks.

PRECAUTIONS: Lactulose syrup contains galactose (less than 2.2 g./15 ml.) and lactose (less than 1.2 g./15 ml.) and it should be used with caution in diabetics. There have been conflicting reports about the concomitant use of neomycin and lactulose syrup. Theoretically, the elimination of certain colonic bacteria by neomycin and possibly other anti-infective agents may interfere with the desired degradation of lactulose and thus prevent the acidification of colonic contents. Thus the status of the lactulose-treated patient should be closely monitored in the event of concomitant oral anti-infective therapy. Other laxatives should not be used especially during the initial phase of therapy for portal-systemic encephalopathy because the loose stools resulting from their use may falsely suggest that adequate Cephulac dosage has been achieved. In the overall management of portal-systemic encephalopathy it should be recognized that there is serious underlying liver disease with complications such as electrolyte disturbance (e.g., hypokalemia) for which other specific therapy may be required.

ADVERSE REACTIONS: Cephulac may produce gaseous distention with flatulence or belching and abdominal discomfort such as cramping in about 20% of patients. Excessive dosage can lead to diarrhea. Nausea and vomiting have been reported infrequently.

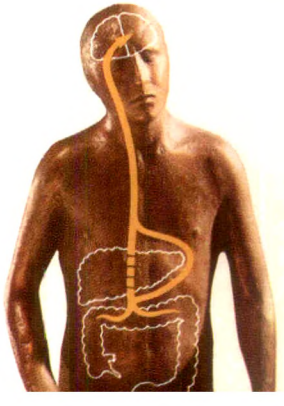
DOSAGE AND ADMINISTRATION: The usual dosage is 2 to 3 tablespoonfuls (30 to 45 ml., containing 20 g. to 30 g. of lactulose) three or four times daily. The dosage may be adjusted every day or two to produce 2 or 3 soft stools daily. Hourly doses of 30 to 45 ml. of Cephulac may be used to induce the rapid laxation indicated in the initial phase of the therapy of portal-systemic encephalopathy. When the laxative effect has been achieved, the dose of Cephulac may then be reduced to the recommended daily dose. Improvement in the patient's condition may occur within 24 hours but may not begin before 48 hours or even later. Continuous long-term therapy is indicated to lessen the severity and prevent the recurrence of portal-systemic encephalopathy. The dose of Cephulac for this purpose is the same as the recommended daily dose.

Product Information as of August, 1975

References:

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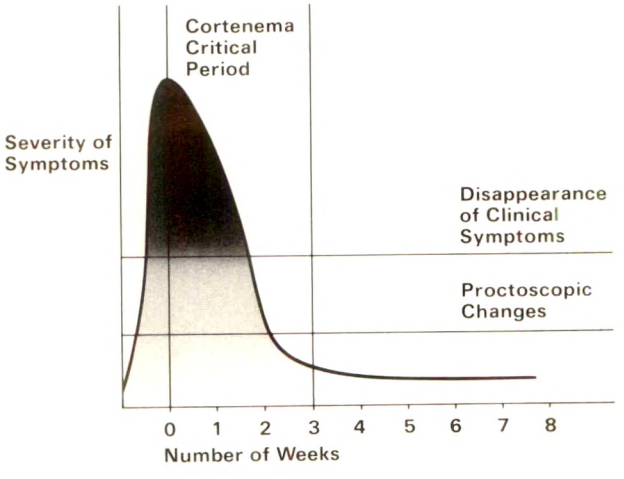
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Effects of Enteric Microbial Overgrowth on Small Intestinal Ultrastructure in the Rat

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The ultrastructural effects of bacterial proliferation in the upper gastrointestinal tract induced by intraperitoneal injections of mecamylamine HCl were investigated in rats. We found increased populations of nonspecific enteric bacteria in the lumen of the upper small intestine and ultrastructural abnormalities in the absorptive epithelial cells, including increased numbers of lysosomal vacular structures, fused microvilli and dilated endoplasmic reticulum. The bacteria did not penetrate into the damaged mucosal cells and so actual cytoplasmic infiltration is apparently not required in order to cause these ultrastructural changes. The alterations were not merely due to the pharmacologic agent we used, mecamylamine, since rats with subnormal numbers of enteric bacteria in the upper small intestine, whether subjected to the course of the drug or not, did not display the ultrastructural changes noted above. Concomitant with increased numbers of enteric bacteria in the small intestine, there were increased concentrations of deconjugated bile salts and decreased absorption of glucose. These findings are compatible with the following hypothetical sequence of pathogenesis: mecamylamine → intestinal stasis → bacterial overgrowth → deconjugation of the bile salts → ultrastructural alterations.

INTRODUCTION

Acute diarrhea has been attributed to overgrowth of certain microbial inhabitants of the gut in both adults[1-4] and children.[5-10] A variety of complications have been associated with bacterial overpopulation, including monosaccharide intolerance and *pneumatosis intestinalis*.[11-14] The pathophysiology of these intestinal dysfunctions is poorly understood. For example: are the overpopulating bacteria necessarily classical enteropathogens or merely normal flora that have been permitted to proliferate? Is

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TABLE I

CORRECTNESS OF INTERPRETATION OF ELECTRON MICROGRAPHS

Control		Experimental		Combined	
n = 60		n = 46		n = 106	
Right	Wrong	Right	Wrong	Right	Wrong
54	6	38	8	92	14

$P < 0.01$ in all cases.

Comparison of correct and incorrect judgments concerning the source of 106 electron micrographs examined in random order. The P value indicates the probability that the given number occurred by chance.

penetration into the cytoplasm of the mucosal epithelial cells a requisite for all changes?

We examined the ultrastructure of the absorptive epithelium in upper segments of the rat small intestine following a course of intraperitoneal injections of mecamylamine, a beta-adrenergic blocking agent reported by others to reduce intestinal motility to near-stasis.[15] Simultaneously, we measured the populations of bacteria present in the small intestinal lumen after such a course of treatment. Our results suggest that elevated populations of colonic and fecal bacteria in the small intestine cause focal fine structural changes in absorptive epithelial cells without actually invading the intestinal mucosa. Concomitantly, the concentration of deconjugated bile salts in the small intestinal fluid was increased after mecamylamine treatment. Abnormalities in intestinal transport capacity which also occurred are reported elsewhere.[16]

MATERIALS AND METHODS

Animal and drug treatments:—Mecamylamine HCl (Sigma Chemical Co., St. Louis, MO) in doses of 20 mg./kg. was injected intraperitoneally twice a day for three days into juvenile rats weighing 70-85 gm. Control rats were injected with a 0.9% NaCl solution. Both groups of animals were fed Purina Chow *ad libitum*. The same experimental procedures were performed on "germ-free" rats (strain CD, Charles River Breeding Labs., Wilmington, MA), weighing 60-80 gm. These rats were delivered to the laboratory under aseptic conditions, which were maintained throughout the course of the experiment. The rats were fed sterilized food and water, and injected with mecamylamine or NaCl without violating aseptic technic. Thus, four groups of animals were studied: 1. randomly bred rats from our laboratory colony, injected with mecamylamine HCl; 2. rats from the same colony, injected with NaCl; 3. Charles River germ-free rats, injected with mecamylamine HCl and 4. Charles River germ-free rats, injected with NaCl. We shall refer to these four groups respectively as "regular MCA", "regular control", "low-germ MCA" and "low-germ control".

Bacteriological and bile salt assays:—Intestinal fluid taken from all four groups of animals was cultured for bacteriological analysis and was assayed for bile salt concentrations. The intestinal flora were measured as follows: the entire intestine was removed and its length measured. A specific segment, beginning at the ligament of Treitz and continuing 20 cm. distally, was then cut out and washed with 10 ml. sterile water into a sterile anaport vial (prereduced container) for "wash" cultures. The "wash" preparations were shaken vigorously for 10 minutes, then serially diluted and cultured as follows:

Aliquots taken from each of the homogenates were serially diluted to the following concentrations with reference to the original homogenate: 10^{-1}, 10^{-3}, 10^{-5} and 10^{-9}. One one hundreth milliliter of each dilution was plated onto the following

TABLE II

BILE SALTS CONCENTRATION IN JEJUNAL FLUID IN MECAMYLAMINE TREATED RATS

Group	Treatment	No. of rats	Conjugated	Deconjugated	Ratio
R	mecamylamine	8	0.82 ± .15*	0.59 ± .17	1.38
R	control/saline	8	0.59 ± .16	0.31 ± .13	1.59
LG	mecamylamine	7	1.70 ± .61*	nondetectable	–
LG	control/saline	8	0.97 ± .13	nondetectable	–

* $P < 0.05$
"R", regular breeding conditions; "LG", low-germ breeding conditions.

media: 1. Under anaerobic conditions, a. Schlaeder agar plates; b. phenylethyl alcohol medium plates; c. tomato juice plates; d. lactobacillus species plates; e. RGCA (rumen-fluid-glucose-cellobiose agar) roll tubes; f. TSN (trypticase-sulfate-neomycin agar) pour plates. 2. Under aerobic conditions, a. blood agar plates; b. eosin methylene blue plates; c. tomato juice plates; d. lactobacillus species plates; e. trypticase soy agar plates. Colony counts of each organism found were performed on the above media and identification was carried to genus, and when possible, to species.[17-19]

Bile salts were assayed by thin-layer chromatography from the "wash" portion of intestinal fluid.[20].

Electron microscopy:—Tissue samples for electron microscopy were taken from the jejunum from all four groups of animals within two hours after the final injection. Each animal was anesthetized with Nembutal (40 mg./kg.) and the small intestine was surgically exposed. A sample of tissue was cut at a point approximately 20 cm. distal to the pylorus. This sample was treated by one of two methods.

In the first method, a transverse section was cut and immediately immersed in 2.5% glutaraldehyde in 0.5 M cacodylate buffer, pH 7.2, at 0-4° C. After primary fixation for one hour, the tissues were further processed by an accelerated method.[21] Post fixation was carried out for 15 minutes in cold 1% osmium tetroxide in 0.1 M phosphate buffer, pH 7.4. Sucrose was added to this buffer to make it isotonic (310 mOsM). The samples were then washed in cold buffer, dehydrated in graded series of ethanols and embedded in Epon.

In the second method, the small intestine was first intubated in the duodenum, flushed with buffer and then with buffered fixative. In this case, the buffer consisted of 310 mOsM phosphate, pH 7.2 and the fixative was 2.5% glutaraldehyde in this buffer. A transverse section was then taken from the jejunum, immersed in fresh fixative for one hour and thereafter prepared and embedded as above.

Thick sections of epoxy-embedded material were stained with toluidene blue and examined in the light microscope. The blocks were then oriented so that thin sections would be taken of absorptive epithelial cells from the tops and sides of a villus. Thin sections were stained with uranyl acetate and lead hydroxide. Electron microscopy was done with an RCA EMU-3G electron microscope and a JEOL JEM-100 electron microscope.

Blind experimental analysis was carried out in which the investigator was un-

TABLE III

BACTERIAL POPULATIONS IN INTESTINAL FLUID OF JEJUNUM
(μ MOLES/ML)

Injection	No.	Conditions	Anaerobic	Aerobic
			(log/ml.)	
NaCl	12	R	5.06 ± 0.01	4.46 ± 1.07
MCA	11	R	8.37 ± 0.55**	5.06 ± 1.16
NaCl	8	LG	2.19 ± 3.45	2.58 ± 2.24
MCA	7	LG	4.28 ± 4.22	3.33 ± 2.11

* $P < 0.01$ compared with regular control.

"Injection" was made with physiological saline (NaCl) or with 20 mg./kg. mecamylamine HCl (MCA). The rats were bred and maintained under regular (R) or low-germ (LG) conditions.

aware of the treatment to which the rats were previously subjected. Grids were examined in random order, and the micrographs obtained were randomly combined. Each coded micrograph was judged to be from control or experimental material. After decoding, the correctness of judgment was estimated by a nonparametric "sign test."[22] A P value of less than 0.05 was taken to indicate satisfactory judgment (Table I).

RESULTS

Bacterial flora:—In "regular" rats a significant increase in the population of anaerobic intestinal flora was observed in the jejunal segment at the ligament of Treitz in animals treated with mecamylamine (Table II). There was no significant difference, however, in the mean log aerobic bacterial counts in the two sets of animals. The predominant taxa of organisms found were anaerobic *Lactobacilli, bacteroides, Clostridia* and *Diphtheroides.*

In our hands, the small intestines of the Charles River stock CD rats were found not to be truly gnotobiotic, although their total bacterial populations were very low in comparison with those of regular animals (Table III). Therefore, we shall refer to them as "low-germ" animals rather than "germ-free" animals. It should be noted that absolute gnotobiosis in the small intestine is not critical for the experimental design of the present study as it would be, for instance, in an immunological investigation. The lower than normal bacterial population of intestinal bacteria found in the low-germ animals was employed as a base line to which changes caused by mecamylamine treatment could be compared.

In low-germ MCA rats, there was no significant increase in intestinal bacteria as compared with low-germ control rats (Table III). Only one of the seven mecamylamine treated rats, however, had no anaerobic bacteria and another had no aerobic bacteria. The remaining rats had less than 10^5 organism/ml. In contrast, three of eight low-germ controls had no anaerobic growth, and four of eight had no aerobic organisms. The remaining animals had less than 10^4 organisms/ml. In low-germ rats, the predominant organisms were *Lactobacilli, bacteroides* and *Corynebacterium;* very few *Clostridia* or enterococci were found.

Bile salts:—Deconjugated bile salts increased significantly in mecamylamine-treated regular rats (Table II), whereas in low-germ rats, there were no detectable con-

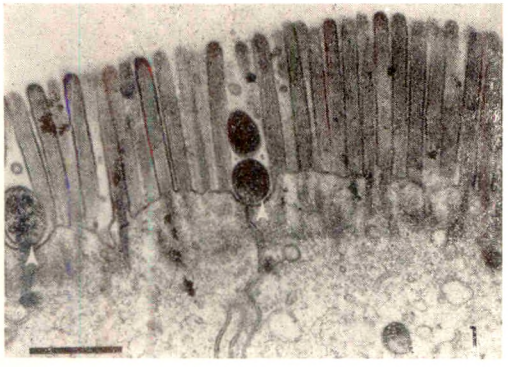


Fig. 1—Deepest observed penetration of intestinal microorganisms (*white arrowheads*) in the jejunum of mecamylamine-treated rats. No microorganisms were found to have penetrated into the cytoplasm or into the intercellular spaces of the mucosal epithelium. Bar = one micron.

centrations of deconjugated bile salts. The concentration of conjugated bile salts always increased by mecamylamine treatment in regular as well as low-germ rats. The deconjugated bile salts most frequently found were cholate, deoxycholate and chenodeoxycholate. The conjugated bile salts were taurocholate, glycocholate, taurodeoxycholate and taurochenodeoxycholate.

Electron microscopy:—Under the electron microscope, micro-organisms adherent to the microvilli of epithelial cells were observed much more frequently in sections taken from the regular mecamylamine treated rats than in those taken from controls. Bacteria were found lodged between microvilli but none were found to have penetrated into the cytoplasm of the absorptive epithelial cells, or into the intercellular spaces between adjacent epithelial cells. Figure 1 shows cross-sectional profiles of the micro-organisms which represent the deepest penetration observed, namely, to the apical plasma membrane between neigboring microvilli.

Focal ultrastructural changes were noted in many of the absorptive epithelial cells in MCA regular rats; they were restricted to single cells or to a region of cells adjacent to cells of normal appearance. The ultrastructural differences, although subtle, were seen consistently in comparisons of control with experimental tissue and a statistical analysis of the validity of these observations is given in Table I.

Many microvilli in cells of the intestinal mucosa of rats treated with mecamylamine were "twinned"; two adjacent microvilli appeared to be fused at the base but not at their apexes, to form a Y-shaped structure (Fig. 2). This abnormality of the mucosal surface was observed previously in other forms of experimentally induced diarrhea and stress.[23] The frequency of twinned microvilli in MCA regular rats was $3.7 \pm 0.04\%$ as compared with $1.4 \pm 0.50\%$ in controls ($P < 0.01$). Furthermore, the length of fusion (distance between intermicrovillous plasma membrane and the point of divergence of the apical parts of the twinned microvilli) in the controls was only slightly greater than zero, whereas in the experimental tissue, it was often more than 50% of the entire length of the microvilli.

Mitochondria and endoplasmic reticulum (ER) were abnormal in intestinal epithelial cells of mecamylamine-treated regular rats as compared with controls. Figures 3 an 4 show comparable fields of the apical regions of cells from control and treated animals, respectively. In Figure 3, the tissue is unremarkable; mitochondria and ER cisternae are of normal size and configuration. By contrast, the endoplasmic reticulum in experimental tissue (Fig. 4) is generally dilated and the mitochondria are swollen and show loss of matrix density.

In experimental tissue (from MCA regular rats), nuclear outlines were often irregular (thus the nucleus itself misshapen), and the space between the inner and outer membranes of the nuclear envelope



Fig. 2—"Twinned" microvilli (arrowhead), showing approximately 60% basal fusion, observed in mecamylamine-treated rats.

was widened to approximately 60 nm. (Fig. 5). Such nuclei seemed to contain proportionately more heterochromatin than observed in nuclei of control tissue. The profiles of nuclei in control tissue were smooth, with few indentations and in the nuclear envelope a normal space was maintained between its inner and outer membranes (Fig. 6).

Damage to the endoplasmic reticulum and to mitochondria may have led to the formation of secondary lysosomes (autographic vacuoles) in some of the affected cells. For example, in Figure 7, remnants of the original mitochondrial structure can be discerned within a secondary lysosome.

In low-germ mecamylamine-treated rats, no micro-organisms were seen adherent to or lodged between microvilli of absorptive epithelial cells. In these rats no ultrastructural differences were apparent between mecamylamine treated animals and saline injected controls. Microvilli were normal both in numbers and structure and no marked evidence of twinning was noted. Mitochondria showed no signs of swelling; there was no dilation of ER and no separation of the nuclear envelope.

Comment

The present study suggests that increased populations of nonspecific enterobacteria in the upper small intestine cause ultrastructural changes in the epithelium without apparent invasion into the epithelial cells; fine structural changes included fusion of microvilli and thereby a reduction in the effective absorptive area of the intestine and alterations in endoplasmic reticulum and lysosomes. These morphological changes were positively correlated with increased luminal bacterial populations. Penetration of the bacteria into the epithelium, however, was not observed. On the other hand, when bacterial populations in the upper bowel were low, there were no ultrastructural changes. In the low-germ treated with mecamylamine, the epithelium

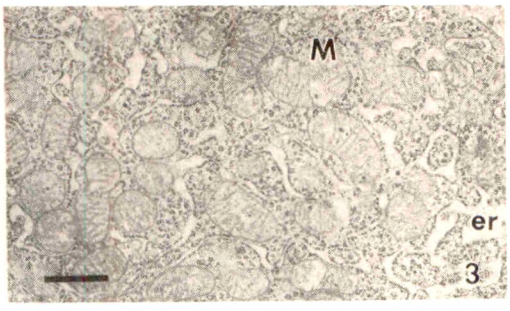


Fig. 3

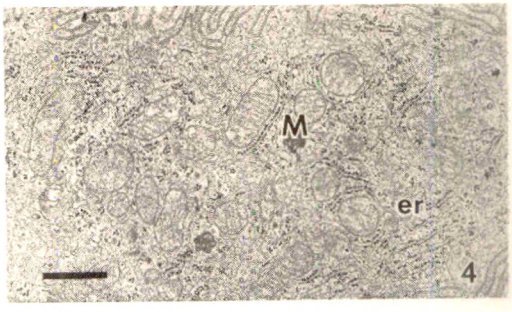


Fig. 4

Figs. 3 and 4—Comparable fields of apical cytoplasm of intestinal mucosa from experimental and control animals, shown at same magnification. Mitochondria (*M*) in experimental tissue (Fig. 3) are swollen and show loss of matrix density; endoplasmic reticulum (*er*) is dilated. These organelles are unremarkable.

was also structurally normal, strongly suggesting that the changes observed probably are not merely due to the side-effects of the particular drug used. The abnormalities observed were also similar to those which are induced experimentally in animals with bacterial proliferation by intestinal blind loops.[24, 26] Elsewhere, we reported physiological alterations in the intestinal transport of glucose, 3-0-methyl-glucose, sodium and amino acids associated with small intestinal proliferation of colonic and fecal bacteria and bile salt deconjugation, achieved by administration of mecamylamine or other beta-adrenergic blocking agents.[16]

The ultrastructural and functional changes seen in the small intestine of the regular MCA rats may, in part, be related to the effect of proliferation of bacterial anaerobes on bile salt metabolism. In the present study bacterial proliferation was accompanied by bile salt deconjugation; this is known to produce fine structural mucosal damage,[27] as well as inhibition of absorption of electrolytes and glucose along with inactivation of adenosine triphosphatase.[28] The injurious effects of bile salts have also been ascribed to the production of bacterial metabolites which inhibit conjugation of cholic acid[29] and to bile salt depletion.[30] The presence of high concentrations of conjugated bile salts in our experiments may have, to some extent, modified the injurious effects of deconjugated bile salts.[31, 32]

The type and the number of bacteria colonizing the upper bowel may also play a role in the induction of abnormalities in the intestine. Both quantitative and qualitative differences in small bowel bacteria may account for various degrees of bile salt deconjugation[33] and the production of other factors which may also be injurious to the small intestine.[34-36] The third order magnitude differences in the anaerobic bacterial counts between regular and low-germ MCA rats may account for the failure to demonstrate deconjugation of bile salts and alterations in intestinal ultrastructure in low-germ MCA rats. In addition, differences in the type of bacterial flora, mainly the absence of significant numbers of clostridia and enterococci in the low-germ rat, may have prevented formation of injurious factors.

The overgrowth of the microbial population of the small intestine by colonic and fecal flora induced by mecamylamine treatment in rats did not result in penetration or invasion of bacteria into the epi-

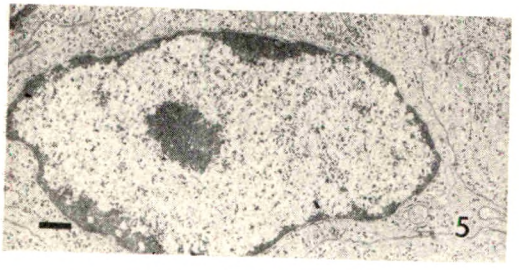


Fig. 5

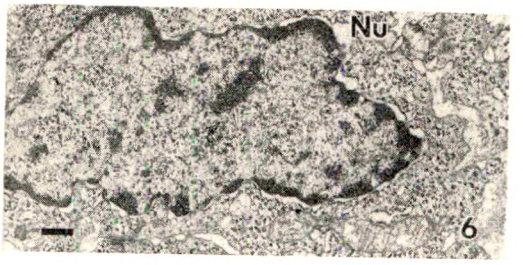


Fig. 6

Figs. 5 and 6—Comparison of nuclei in epithelial cells of control (Fig. 5) and experimental (Fig. 6) tissue. In the latter, the nuclear profile is more irregular, and the space between the inner and outer membranes of the nuclear envelope (*Nu*) is widened. Bar = one micron.

thelial absorptive cell cytoplasm of the upper intestinal tract. Therefore, the pathogenesis of the structural and functional abnormalities observed did not appear to be like those caused by a classic enteropathogen[37] or a viral agent.[38] Some of the changes in intestinal function induced by mecamylamine, however, could have been initiated by invasion of bacteria in the lower intestine where organisms have been observed at the submucosa and *muscularis*.[15] Inflammatory reactions resulting from this invasive process may release prostaglandins[39] and these compounds in turn may induce jejunal abnormalities.[40] Furthermore, we cannot rule out the possibility that some of the effects of overpopulating the upper small bowel with bacteria by mecamylamine may have resulted from other injurious factors such as fatty acids[34] or alcohol[36] or from the production of enterotoxin,[41] by any one of the organisms found. In addition to the common enterotoxin producing strains of *Escherichia coli*, other coliform bacterial species have been found to have toxigenic properties. Recently, *Klebsiella* was shown to evoke a positive fluid response in ileal loops and induce abnormalities of intestinal structure.[42] Toxigenic strains of *Klebsiella pneumoniae, azoenge* and *cloacae* were similar to *E. coli* in that they elaborated heat stable or heat labile forms of toxins.[43]

The ultrastructural damage can be characterized as focal, subtle and sublethal. We think it likely that any of these forms of damage is reversible. It should be noted that other studies frequently showed ultrastructural damage to the intestinal mucosa where there was no histological abnormality evident in the light microscope.[24, 44, 45]

Trump et al[46] have proposed a new method of pathological analysis of human tissues. In a schema of progressive cellular responses to injury as seen at the ultrastructural level, the authors characterize a "stage 2" response as sublethal and reversible and using the proximal convoluted tubule epithelium as a model, list the following ultrastructural changes characteristic of this stage: irregular nuclear profile, swollen mitochondria, loss of mitochondrial granules, dilated endoplasmic reticulum, and heterochromatization. It seems likely that the fine structural changes observed in intestinal epithelial cells in the present study also represent a "stage 2" response to an insult (elevated concentrations of unconjugated bile salts, secondary to bacterial overpopulation), a stage in pathogenesis which is early and reversible.

Our observations suggest that the specific organelle affected is the cell membrane. All the abnormalities observed were in the membranous elements of the cell:

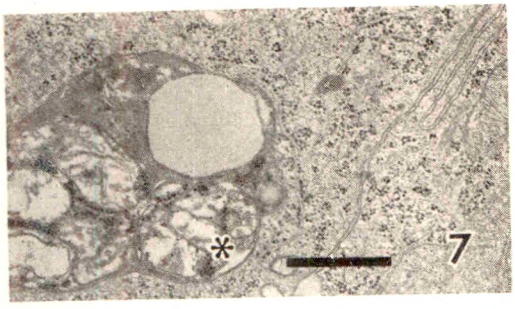


Fig. 7—Secondary lysosome (autophagic vacuole) observed in experimental tissue. Remnants of mitochondrial structure (*) can be observed. Bar = one micron.

microvilli, mitochondria, endoplasmic reticulum, nuclear envelope. This is not surprising, given the emulsifying properties of free bile salts and the great dependence of the unit membrane on the structural integrity of its phospholipids, according to the current fluid mosaic model. This concept is supported by recent work which showed that deconjugated bile salts and other detergents principally affect the membranes of epithelial cells.[31, 32]

Although the mechanism of bacterial proliferation in our rat experimental model probably has little resemblance to the causes of diarrhea or colonic and fecal overpopulation in clinical situations,[6, 13, 47] there are numerous parallels that we think make this preparation of value. The data further substantiate that through a variety of mechanisms,[48] a wide spectrum of enteric microorganisms may alter intestinal function when present in excessive numbers in the small intestine.[48] Whatever the reason, small bowel colonization with enteric microflora may aggravate the alterations in intestinal function and prolong and worsen the disease.[13, 48]

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Studies of the Kinetics of Purified Conjugated Bilirubin-^{3}H in the Rat

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Radio-labeled conjugated bilirubin was purified from rat bile by affinity chromatography. Following the intravenous injection of tracer doses of this material, the initial fractional plasma disappearance rate of conjugated bilirubin-^{3}H in the normal Sprague-Dawley rat was found to be approximately 50% faster than that for unconjugated bilirubin-^{3}H (0.51 ± 0.04 [SE] vs. 0.35 ± 0.02 min.$^{-1}$; $P < .001$). Hepatic recovery studies in the rat indicated that, over the first four minutes after injection, disappearance of cholephilic anions from plasma is accounted for almost entirely by hepatic uptake. Hence, these studies demonstrate that hepatic uptake of conjugated bilirubin is substantially faster than that of unconjugated bilirubin. Net hepatic clearance of conjugated bilirubin in normal rats was three-fold greater than that of unconjugated bilirubin (0.94 ± 0.16 vs. 0.30 ± 0.03 ml./min./100 gm. body weight; $P < .001$), presumably reflecting both the more rapid hepatic uptake and the ability of the former pigment to by-pass the conjugation step. Hepatic uptake of conjugated bilirubin was shown to be inhibited by unconjugated bilirubin, sulfobromophthalein and indocyanine green but not by glycocholate. These observations cannot be explained by simple diffusion and suggest that the hepatic uptake mechanism for conjugated bilirubin is the same as that for the unconjugated pigment.

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* Mr. Shupeck was the recipient of a Travel Award in the 1977 Student Research Competition of the American Gastroenterological Association and presented this work at the Association's Annual Meeting in Toronto, Canada, 18 May 1977.[1]

Introduction

Despite recent advances in elucidation of the chemical structures of bilirubin conjugates,[2] investigation of the metabolism of conjugated bilirubin has been hampered heretofore by the lack of suitable preparations of purified conjugated pigments. The recent development of a simple technic for

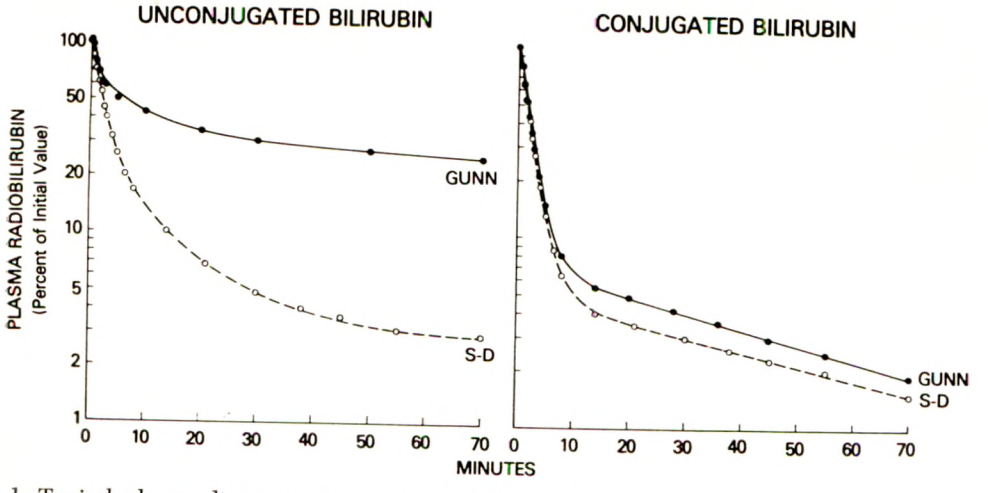


Fig. 1—Typical plasma disappearance curves of tritium labeled unconjugated and conjugated bilirubin in normal Sprague-Dawley and jaundiced Gunn rats.

the isolation of radiolabeled conjugated bilirubin from rat bile[3] has greatly facilitated physiologic and metabolic studies not previously feasible. This report describes the results of plasma disappearance studies of ^{3}H-conjugated bilirubin in the rat. These represent the first physiologic studies with purified bilirubin conjugates to be reported.

Methods

Preparation of ^{3}H-conjugated bilirubin:—Conjugated bilirubin-^{3}H (CB-^{3}H) was isolated from the bile of Wistar-R rats (Université Catholique de Louvain) by affinity chromatography over albumin-agarose, chloroform-methanol (2:1, v:v) extraction and Sephadex G-25 column chromatography, as previously described.[3] Prior to collection of bile, the rats were injected with δ-aminolevulinic acid-2,3-^{3}H (33 mCi/m mole; Schwartz/Mann), a precursor of hepatic "early labeled" bilirubin.[4] The CB-^{3}H prepared for these studies consisted of an equimolar mixture of mono- and diglucuronides, as determined by thin layer chromatography of ethyl anthranilate azopigments.[5] The pigment was free of phospholipid, cholesterol and protein but did contain a trace of residual bile acid (molar ratio bile acid:bilirubin $<$ 0.1:1, compared to 11.1:1 in initial bile sample).[3] Its specific activity was 50 mCi/m mole. Material was aliquoted into individual dosage vials, each containing 0.5-0.8 μCi, lyophilized and stored in vacuo, at −20° C, in the dark, prior to use. For some studies, unconjugated bilirubin-^{3}H (UCB-^{3}H) (100 mCi/m mole) was prepared biosynthetically in bile fistula dogs.[6]

Plasma disappearance studies:—All plasma disappearance studies were performed in pentobarbital-anesthetized male Sprague-Dawley (Taconic Farms, Inc., Germantown, NY) or jaundiced Gunn (Animal Resources Branch, National Institutes of Health) rats weighing 280-400 gm., prepared with jugular vein and carotid artery canulas.[7] CB-^{3}H was dissolved in 1.0 ml. 1 N saline and UCB-^{3}H in 100 μl 0.1 M NaOH followed by 1 ml. rat plasma prior to intravenous injection. All intravenous injections were through the jugular vein catheter, following which blood samples were collected from the carotid artery. Procedures for sample collection, preparation and radioisotope counting, as well as physiologic monitoring during each study were as previously described.[7]

TABLE I

PLASMA DISAPPEARANCE RATES AND HEPATIC RECOVERY DATA FOR FOUR CHOLEPHILIC ORGANIC ANIONS

Test substance	Plasma fractional disappearance rate (k, min.$^{-1}$)		Hepatic recovery (% predicted)*	
	mean ± SE	n	mean ± SE	n
Unconjugated bilirubin-^{3}H	0.35 ± 0.02	29	99.9 ± 5.6	15
Conjugated bilirubin-^{3}H	0.51 ± 0.04	5	94.1 ± 4.0	7
Indocyanine Green	0.52 ± 0.02	5	97.9 ± 5.0	12
Sulfobromophthalein-^{35}S	0.94 ± 0.01	5	86.8 ± 5.9	14

* % predicted = 100 X (quantity of test substance measured in liver at time t after injection) ÷ (Dose X [1-e^{-kt}]), for t ≤ 4 minutes.

Two protocols were employed. In protocol A, 3-5 μCi of CB-^{3}H or UCB-^{3}H were injected and blood samples were obtained at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4, 5, 8, 14 20, 28, 37, 45, 55 and 70 minutes. Plasma disappearance curves of CB-^{3}H were obtained in five normal Sprague-Dawley and six jaundiced Gunn rats. These studies were compared with UCB-^{3}H disappearance curves obtained in eight Sprague-Dawley and six Gunn rats. Curves were fitted to sums of two (CB-^{3}H) or three (UCB-^{3}H) exponential functions on a Univac 1108 digital computer, using the Simulation, Analysis and Modeling program[8] and the results were used to calculate net hepatic bilirubin clearance (C_{BR}, ml./min./100 gm. body weight), as previously described.[9]

In protocol B, radioactivity was determined in seven to nine plasma samples obtained at 20-30 second intervals for three and a half minutes following injection of 0.5-0.8 μCi CB-^{3}H. In some studies, nonradioactive unconjugated bilirubin (UCB), sulfobromophthalein (BSP), indocyanine green (ICG) or sodium glycocholate was injected simultaneously with the CB-^{3}H. In all the studies under protocol B, a semilogarithmic plot of the data points over the first three minutes was linear and the plasma fractional disappearance rate of CB-^{3}H (k, min.$^{-1}$) was calculated from these data by the method of least squares. In seven studies of protocol B, the liver was rapidly excised at four minutes after injection, homogenized and its total CB-^{3}H content determined.[7] After correction for intrahepatic plasma content, the radioactivity recovered in these livers was compared with the quantity of CB-^{3}H which had left the plasma by four minutes [given by Dose X (1-e^{-kt})], using an equation derived previously.[7]

RESULTS

Typical plasma disappearance curves obtained under protocol A are illustrated in Figure 1. Clearance of conjugated bilirubin was, not unexpectedly, much greater than that of unconjugated bilirubin in the glucuronyl transferase deficient Gunn rats (0.81 ± 0.08 [SE] vs. 0.005 ± 0.0004 ml./min./100 gm. body weight; $P < .001$). Clearance of conjugated bilirubin was also more rapid than that of unconjugated bilirubin in the normal Sprague-Dawley animals (0.94 ± 0.16 vs. 0.30 ± 0.03 ml./min./100 gm. body weight; $P < .001$). Clearance of conjugated bilirubin did not significantly differ between the Gunn and

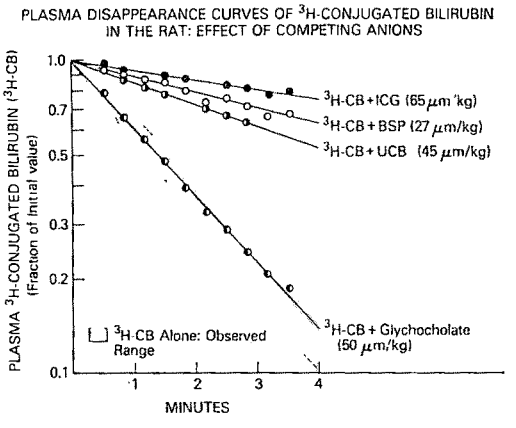


Fig. 2—Plasma disappearance curves of ³H-conjugated bilirubin (CB-³H) administered intravenously to normal Sprague-Dawley rats simultaneously with the indicated quantities of unconjugated bilirubin (UCB), sulfobromophthalein (BSP), indocyanine green (ICG) or sodium glycocholate. Stippled area denotes the observed range of curves for CH-³H administered alone in five animals.

Sprague-Dawley animals ($P > .4$) confirming that the defect in bilirubin metabolism in the former strain is restricted to the conjugation step.

Fractional plasma disappearance rates and hepatic recovery of injected CB-³H at four minutes are presented in Table I, for studies performed in normal Sprague-Dawley rats. Corresponding data for UCB-³H, BSP and ICG from a previously published study from this laboratory[7] are presented solely for comparison. Note that the plasma fractional disappearance rate for CB-³H is approximately 50% greater than that for UCB-³H ($P < .001$) The hepatic recovery data in Table I indicate that, in the normal rat during the first three minutes after injection, the disappearance of these cholephilic organic anions from plasma is accounted for virtually completely by hepatic uptake. Hence, these observations indicate that hepatic uptake of conjugated bilirubin is substantially faster than that of unconjugated bilirubin in the rat.

Results of competition studies are illustrated in Figure 2. The hepatic uptake of CB-³H was appreciably reduced by simultaneous injection of 65 μM/kg. ICG ($k = 0.07$ min.$^{-1}$), 27 μM/kg. BSP ($k = 0.12$ min.$^{-1}$) and 45 μM/kg. UCB ($k = 0.16$-0.27 min.$^{-1}$) but was unaffected by 50 μM/kg. sodium glycocholate ($k = 0.51$ min.$^{-1}$). Mutual competition for hepatic uptake between UCB, ICG and BSP—but not glycocholate—has been demonstrated previously.[7]

Comment

The movement of bilirubin from blood to bile is conventionally described as occurring in four distinct but related steps.[10] These are: 1. hepatocellular uptake of unconjugated bilirubin; 2. binding of unconjugated bilirubin to specific intracellular binding proteins; 3. conjugation by microsomal enzymes, principally bilirubin-UDP glucuronyl transferase and 4. prompt active transport of the resulting conjugated bilirubin across the canalicular membrane into the biliary tract, so that little conjugated bilirubin accumulates within the liver cell.

This scheme implies that the intracellular binding proteins play little or no role in the transcellular movement of conjugated bilirubin, that bilirubin conjugation occurs exclusively as a result of microsomal activity, and that conjugation and biliary excretion of the conjugate are both anatomically and biochemically separate processes. Furthermore, this scheme ignores the existence of a hepatocellular uptake mechanism for any conjugated bilirubin which has gained access to the peripheral circulation.

Recent studies of the metabolism of conjugated bilirubin have added new information about several aspects of its hepatic transport and have challenged a number of these older concepts. Thus, Wolkoff, et al have recently reported that sub-

stantial quantities of conjugated bilirubin can, in fact, be detected in the livers of normal rats by thin layer chromatographic technics.[11] This intrahepatic pool of conjugated bilirubin consists virtually exclusively of bilirubin monoglucuronide, despite the demonstration that both the monoglucuronide and diglucuronide of bilirubin have very high affinities for the entire glutathione-S-transferase family of intrahepatic organic anion binding proteins, such as ligandin.[11]

Almost simultaneously, Jansen, et al[12] have presented evidence that although formation of bilirubin monoglucuronide is catalyzed by the microsomal enzyme bilirubin-UDP glucuronyl transferase, the conversion of bilirubin monoglucuronide to diglucuronide is not. Rather, their data suggest that conversion of the monoglucuronide to diglucuronide occurs by the action of a separate transesterase enzyme, located in the canalicular plasma membrane. If bilirubin diglucuronide is, indeed, formed at the canalicular membrane and therefore promptly excreted, this observation may explain the failure of Wolkoff, et al[11] to find significant quantities of diglucuronide within the liver.

In the present study, the plasma kinetics of CB-^{3}H were investigated *in vivo*. The results of protocol A indicated a more rapid clearance of CB-^{3}H than of UCB-^{3}H in the normal rat. While this finding was not qualitatively unexpected, because the injected CB-^{3}H could by-pass the conjugation step, the magnitude of the increase was greater than anticipated. The results of protocol B establish that the initial hepatic uptake for conjugated bilirubin is substantially faster than for the unconjugated pigment, a factor which accounts for part of the increase in net hepatic clearance.

Hepatic uptake of unconjugated bilirubin has been shown to be: 1. saturable, 2. subject to specific, competitive inhibition by compounds such as BSP and ICG but not by bile acids and 3. capable of demonstrating a kinetic phenomenon known as "counter transport."[7] These are the three kinetic properties which, in simpler systems than the intact rat, characterize carrier mediated transport.[13] While the existence of a liver cell membrane carrier transport system for unconjugated bilirubin has not been demonstrated conclusively, preliminary work suggests the isolation of a membrane fraction from rat liver which demonstrates certain of the essential properties of such a hypothetical carrier.[14]

It has not been possible to demonstrate saturability or counter transport for the hepatic uptake of conjugated bilirubin, or to confirm that the apparent inhibition produced by unconjugated bilirubin, BSP and ICG is truly competitive in nature. Such studies would require far greater quantities of purified conjugated bilirubin than it has thus far been possible to isolate. Nevertheless, the studies illustrated in Figure 2 clearly indicate that the entry of conjugated bilirubin into the liver cell cannot be explained by simple diffusion. More particularly, they suggest that the hepatic uptake mechanism for conjugated bilirubin may be the same as that for unconjugated bilirubin.

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Communication from Abroad

Does Secretin Influence Rat Colonic Absorption and Secretion?

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In rats, a secretin (Jorpes) intravenous infusion superimposed on an intracolonic sodium acetate perfusion elicits, with respect to control values, a significant depression of Na^+ absorption (0.16 mEq./h.-0.00 mEq./h.) and mucus secretion (230-40 mg.). When the hormone is superimposed upon an intracolonic infusion of acetic acid, mucus secretion is also significantly inhibited (790-340 mg.). The influence of secretin on organic anion movement was pH related. At pH values of 7.0, absorption was unchanged (0.34-0.33 mEq./h.), at pH values of 2.9, absorption was significantly reduced (0.67-0.41 mEq./h.).

The secretin impairment of colonic mucus secretion could influence the transport of watersoluble (Na^+) and lipid soluble (acetic acid) substances, probably through changes at the "unstirred layer" level.

Introduction

Exocrine pancreas flow rate and electrolyte secretion are the best known effects of secretin.[1] Similar influences have been demonstrated on the small intestine and kidneys.[2] An excitatory effect on gastric pepsin secretion has also been confirmed.[3] On the other hand, the modifications elicited on exocrine pancreas enzyme secretion are now on the way to being understood.[4, 5]

The aim of the present work on rats was to try to determine whether or not secretin, with our experimental model, evokes changes on colonic water electrolyte and mucus movement, triggered by the intraluminal infusion of either sodium acetate or acetic acid solution in this intestinal segment.[6]

Material and Methods

Two series of male Wistar rats, with an average weight of 325 gm. were subjected, under ether anesthesia, to the following experimental protocol: after a mid line laparotomy, the terminal ileum and the right colon were brought out.

Through the former, a metal cannula was inserted with its tip leading to the

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TABLE I

COLONIC PARAMETERS VALUES UNDER SECRETIN PERFUSION

Sodium acetate solution post infusion values

	Volume ml.		Δ Na^+ mEq./hr.		Δ Cl^- mEq./hr.		Δ OA^- mEq./hr.		Mucus weight mg.	
	I	II	I	II	I	II	I	II	I	II
Mean	9	9.6	0.16	0.00	0.01	−0.02	0.34	0.33	230	40
S.D.	0.69	0.91	0.13	0.12	0.07	0.06	0.13	0.11	170	40
S.E.M.	—	—	0.04	0.04	0.03	0.02	0.04	0.03	70	10
Range	7.5-9.9	8.3-10.7	−0.04-0.40	−0.16-0.17	−0.14-0.06	−0.10-0.09	0.08-0.51	0.16-0.48	30-530	0-120
	NS		*		NS		NS		*	

I Sodium acetate 100 mEq./l., NaCl 50 mEq./l., PEG 0.4 gm.%
II Sodium acetate 100 mEq./l., NaCl 50 mEq./l., PEG 0.4 gm.% infused with I.V. Jorpes secretin.

Acetic acid solution post infusion values

	Volume ml.		Δ Na^+ mEq./hr.		Δ Cl^- mEq./hr.		Δ OA^- mEq./hr.		Mucus weight mg.	
	I	II	I	II	I	II	I	II	I	II
Mean	12.41	12.13	−0.47	−0.47	−0.29	−0.18	0.67	0.41	790	340
S.D.	1.60	1.49	0.14	0.17	0.23	0.20	0.15	0.14	100	210
S.E.M.	—	—	0.04	0.06	0.09	0.07	0.04	0.04	40	70
Range	10-15	10-13	−0.64-−0.25	−0.65-−0.21	−0.55-0.10	−0.41-0.13	0.40-0.88	0.26-0.63	640-900	90-720
	NS		NS		NS		**		**	

I Acetic acid 100 mEq./l., NaCl 100 mEq./l., PEG 0.4 gm.%.
II Acetic acid 100 mEq./l., NaCl 100 mEq./l., PEG 0.4 gm.% infused with I.V. Jorpes secretin.
NS: Not significant * $P < 0.05$ ** $P < 0.01$ Δ Final solution − Initial solution − indicates net secretion.

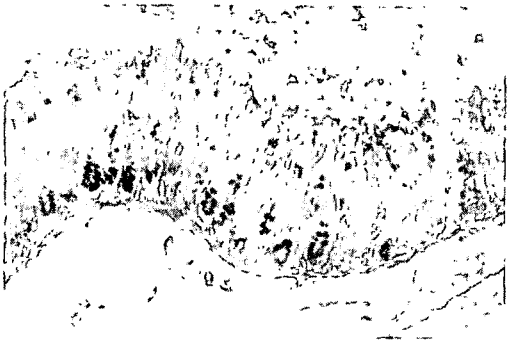


Fig. 1—Right colon mucus depletion after an intracolonic organic anion infusion (Mowry, original magnification x200).



Fig. 2—Inhibition by an I.V. continuous perfusion of secretin of right colon mucus secretion induced by an intracolonic organic anion infusion (Mowry, original magnification x200).

cecum and fixed with ligatures. To prevent reflux of the solution infused to the proximal small intestine, another ligature was placed above the cannula. Cleansing of the colon was then carried out with an enema solution (NaCl 115 mEq./l. KCl 5 mEq./l., CO_3H Na 25 mEq./l.). When this step was completed a plastic cannula was inserted into the rectum and secured in place with a purse string around the anus. Through the metalic cannula in the ileum and with a syringe, 10 ml. of the sodium acetate or acetic acid solution (Table I) was slowly infused into the colon. Clamping of the plastic cannula in the rectum prevented the outside leaking of the infused solutions. Simultaneously, through a polyethylene catheter inserted into the dorso penis vein, a secretin perfusion (GIH, 3.0 C.U./kg./hr.) was started. The hormone, dissolved in isotonic saline, was delivered with an electric peristaltic pump at a 2.0 ml./hr. rate. Either the sodium acetate or acetic acid solution was kept in the colon for a time lapse of 60 minutes. At the end of this period, the secretin perfusion was arrested and the test solution in the colon was recuperated after removing the clamp closing the plastic cannula in the rectum. Immediately after the animals were sacrified and the whole colon was excised and immersed in a 10% calcium formol solution. After paraffin embedding the sections were stained with hematoxylin-eosin, Alcian blue and Mowry (AB/PAS) methods.[7] In the test solutions, the following parameters were measured: 1. volume (PEG was used as nonabsorbable marker)[8]; 2. Na^+ output (flame photometry); 3. chloride output;[9] 4. organic anion output[10]; and 5. mucus weight.

Statistical analyses were performed with the Student "t" test for non-paired values and the nonparametric "U" Mann Whitney test.[11]

Results

Comparison of the present results with those observed previously by us[6] without a superimposed secretin perfusion disclosed the following facts:

When the hormone perfused simultaneously with an intracolonic sodium acetate infusion, net sodium absorption and mucus secretion were significantly depressed (Table I).

When secretin was perfused simultaneously with an intracolonic acetic acid infusion, the Na^+ and Cl^- ion movements remained unchanged but organic anion absorption and mucus secretion fell significantly (Table I).

In both sodium acetate and acetic acid intracolonic infusion series secretin did not elicit any significant change on the perfusate volume (Table I).

Secretin evokes significant changes on the organic anion-induced pattern of mucus distribution in the colonic glands previously discribed by us.[6]

In the right colon, the almost total mucus depletion elicited by OA^- is inhibited by the I.V. secretin perfusion (Figs. 1 and 2). In the left colon, the mucus discharge of the third lower segment of the colonic glands induced by OA^- is notoriously inhibited by the secretin perfused.

Comment

Secretin somehow inhibits the acetic acid or sodium acetate evoked colonic mucus secretion. This is shown by the comparative analysis of the mucus weight values obtained in the series performed with and without a simultaneous intravenous secretin perfusion (Table I).

That this hormone does indeed impair the OA^- induced mucus discharge is confirmed in the above series by the light microscopic and histochemical mucus pattern picture in the colonic glands (Figs. 1 and 2). Under secretin the mucus cells stand out to be less clearly discharged and the whole mucosa, mainly at the level of its surface, gives the impression of being less modified.

Intravenous secretin perfusion elicits a significant fall in the net sodium absorption. As this latter phenomenon is primarily under the influence of an ouabain dependent pump, we could hypothesize two main alternatives. The first one is that secretin does indeed interfere with this pump. This has not been proved up to present. The second possibility is that secretin-evoked retained mucus at the colonic mucosa could act as an ionic exchanger and in this way interfere with the transmural sodium movement.

Further studies should be done in the future in order to ratify or disprove the above mentioned hypotheses. Besides it would be of interest to study other possibilities as it could be the interference of Na^+ recirculation through the paracellular pathway.[12]

Secretin interferes with the colonic absorption of acetic acid (mainly unionized) but not with sodium acetate (ionized); from this we could infer that secretin somehow raises the resistance to the transport of the lipid soluble un-ionized acetic acid. Our purpose is to investigate in the future what changes in the USL [33] in the colon influence the lipid soluble substances absorption. If the above mentioned assumption is confirmed, one would have to admit that secretin, as perhaps it will be found with other gastrointestinal hormones (V.I.P.?), has a modulating role on the intestinal absorption.

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Percutaneous Transhepatic Cholangiography with a Thin Needle

Experience with 25 Cases

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Percutaneous transhepatic cholangiography with a thin needle was successfully employed in 23 of 25 patients with jaundice. A 100% success rate was seen with dilated bile ducts. Not a single complication was observed in our series. With our limited series, it can be assumed that proximal obstruction is more likely to mean neoplasm of either the gallbladder or bile duct, whereas distal obstruction with visualization of dilated cystic duct means either neoplasm of the head of pancreas or metastatic carcinoma.

The jaundiced patient, regardless of etiology, cannot be adequately evaluated with the conventional gallbladder series or intravenous cholangiography. It is also not always possible to differentiate clinically between liver parenchymal and biliary duct obstructive jaundice. Here percutaneous transhepatic cholangiography plays an important role in identifying the location and often the cause of obstruction. Because of a rather high rate of and sometimes seriousness of complication with conventional percutaneous transhepatic cholangiography—that is, with a large needle and with or without catheter—it has never been widely accepted. At Kenmore Mercy hospital, there were only two cases in the three years prior to introduction of skinny needle cholangiography compared to 25 cases referred in the year following (September 1976-August, 1977). A similar increase has been reported in another institute.[1]

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Technic

The patient is first premedicated with Valium®, 5-10 mg. I.M. and an I.V. line is established. After confirming an adequate platelet count, P.T. and P.T.T., a lead marker is placed over the xyphoid (at the level of D-12) and a puncture site is determined about halfway between the right costophrenic angle and the lower margin of the liver, usually the eighth or ninth intercostal space at its mid axillary line. Fluoroscopic control is used.[1-4] This precaution is taken so as not to puncture lung or bowel. After local anesthesia, skin puncture is made and again, under fluoroscopic control, the thin needle is advanced parallel to the x-ray table top and its tip is placed about 4 cm. lateral to the level of D-12 during apnea. Only shallow breathing is allowed. A small amount of Renografin 30 is injected while the needle is slowly with-

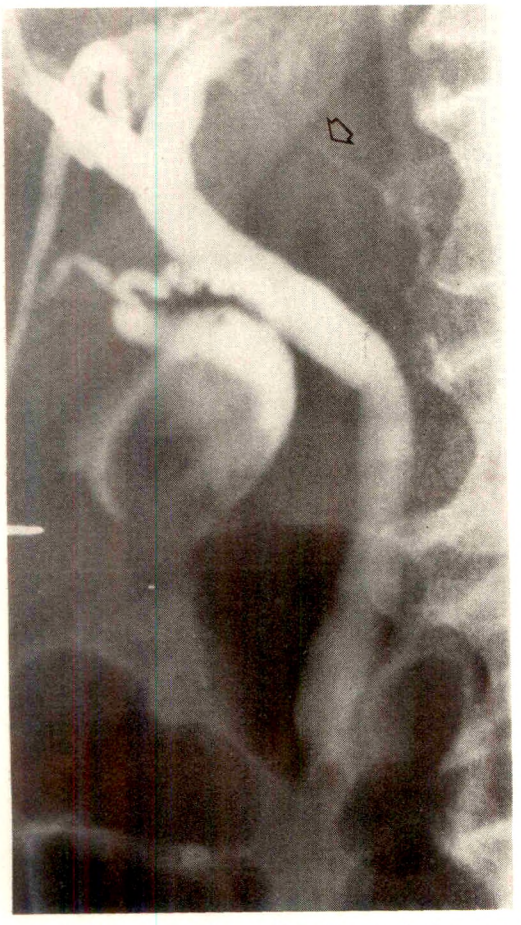


Fig. 1—Stones in the gallbladder and the common bile duct. Lymphatic vessels are well demonstrated (arrow).

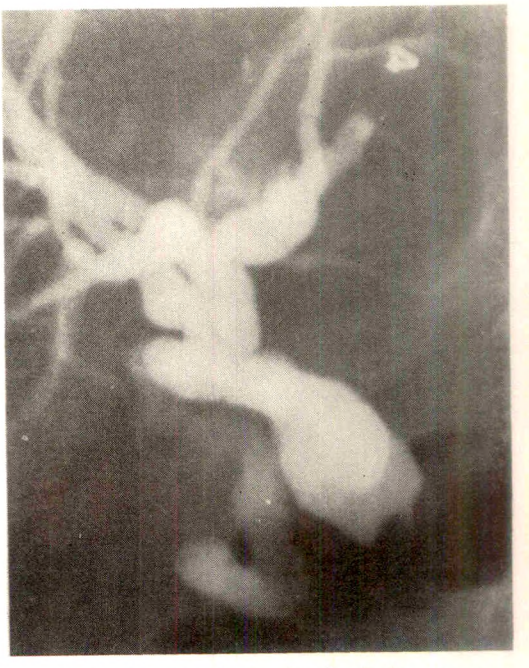


Fig. 2—Carcinoma of the head of the pancreas with visualization of the dilated cystic duct. It appears radiographically more likely as a intrinsic space-occupying lesion of the common bile duct. No involvement was found, however, in the surgical specimen.

drawn under fluoroscopic control. When a biliary duct is entered, slow filling of the duct occurs, whereas when a vein or artery is entered rapid centrifugal clearing of contrast medium occurs. When the parenchyme is filled, puddling of contrast occurs and if lymphatics are punctured, fine linear collection of contrast moves toward the vertebra (Fig. 1). When a dilated duct is found, a sufficient amount of contrast medium is injected and various projections including semi-upright projections should be obtained to delineate the site of obstruction. It has been reported that very often dense inspissated bile prevents contrast medium from filtering through to the site of obstruction.[5] But, if the technic of multiple projections, adequate dye and especially the semi-upright projection are used, the latter problem does not occur. If a bile duct is not entered, additional attempts should be made, angling the tip of the needle anteriorly or posteriorly as many as six times. If a dilated duct is found, antibiotics are given in order to prevent septicemia from shunting between dilated bile ducts and veins.

Results

The biliary tree was satisfactorily visualized in 23 of 25 patients (92%). Among those, 16 of 16 (100%) revealed dilated ducts and seven of nine (77%) showed ducts that were either normal or of small caliber. All 16 patients with dilated

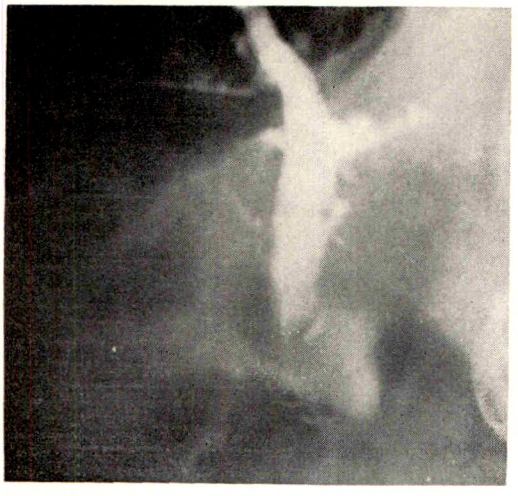


Fig. 3—Carcinoma of the gallbladder with complete occlusion of the proximal bile duct. Fistular formation between the bile duct and the colon.

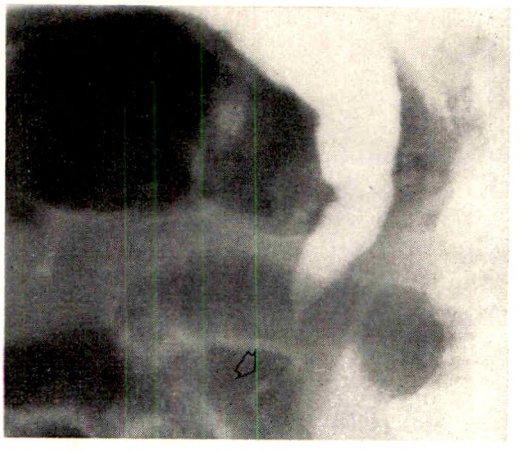


Fig. 4—Carcinoma of the head of the pancreas with a threadlike narrowing, with incomplete occlusion (arrow).

ducts were subsequently operated upon and with the following findings: six had carcinoma of the head of the pancreas; one had carcinoma of the gallbladder; one had carcinoma of the bile duct; two had metastatic disease; five had stones in the common bile duct and one had had a previous ligation of the hepatic duct.

Comment

Because of a high incident rate of serious complications and the necessity of preparing for immediate surgical intervention, conventional PTC has never been widely accepted.[6, 7] Since, however, the introduction of the use of the thin needle there is a higher success rate in visualizing the biliary tree and a lower incidence of serious complications. In our 25 cases during the first year of its use, we have had a 100% (16 of 16) success rate in visualization of dilated bile ducts and 77% in either normal or small caliber ducts. There was not a single complication in our series. It was felt that careful monitoring of the site of puncture and placement of the tip of the needle in the liver under fluoroscopic control has played an important role. Sufficient amount of the contrast medium should be used to delineate the site of obstruction with various projections including semi-upright views. It has been difficult to make histologic diognoses of exact bile duct disease with percutaneous transhepatic cholangiography as reported by others.[5, 8]

With our limited experience, however, carcinoma of the head of pancreas and metastatic disease of the liver hilum showed distal bile duct obstruction with visualization of the dilated cystic duct (Fig. 2), whereas carcinoma of either the gallbladder or the bile duct showed obstruction of the latter to be more proximal (Fig. 3). It has been difficult to differentiate intrinsic defects from extrinsic ones (except stones) due to the limited views available (Fig. 2). We had no difficulty in differentiating benign from malignant lesions. One of the six cases of carcinoma of the head of pancreas had a threadlike smooth narrowing of distal common bile duct 5 cm. long with incomplete occlusion (Fig. 4). Another had a short segment of smooth narrow duct followed by 3 cm. of normal duct to the duodenum. The one patient with carcinoma of the gallbladder had considerable improve-

ment of his jaundice prior to percutaneous transhepatic cholangiography and it was found that a fistula had formed between the bile duct and colon as demonstrated by percutaneous transhepatic cholangiography (Fig. 2). The combined percutaneous transhepatic cholangiography and angiography have been widely used in order to upgrade the diagnosis of carcinoma of the pancreas with different degrees of success.[9, 10] It is our feeling that the use of percutaneous transhepatic cholangiography as an investigative tool for the diagnosis of carcinoma of head of pancreas and angiography for carcinoma of the body and tail of the pancreas without jaundice can upgrade the accuracy of the diagnosis of these two related diseases considerably.

It is worthwhile to mention that endoscopic retrograde cholangiography is a reasonably safe and efficient procedure in evaluating jaundiced patients. We feel, however, that as reported by others,[1] it is a time-consuming expensive and difficult procedure as compared to percutaneous transhepatic cholangiography.

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The Effect of Glucagon on the Exocrine Pancreas

A Review

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Glucagon can depress normal animal and human pancreatic exocrine secretions and modify experimentally-induced pancreatitis in animals. It has yet to be demonstrated that glucagon has any efficacy in the treatment of the diseased pancreas in man. Glucagon might act on the exocrine pancreas by 1. reducing pancreatic blood flow, 2. decreasing gastric secretion, 3. lowering serum calcium levels by the release of calcitonin, 4. acting to inhibit the secretin mechanism, 5. causing a hyperglycemia and 6. degranulating pancreatic acinar cells. While a reduction in pancreatic blood flow, an inhibition of the secretin mechanism and a hyperglycemia seemed to have been ruled out as possible mechanisms of action, there is too little available data to effectively speculate on the mechanism(s) of action of glucagon on the exocrine pancreas.

Introduction

Glucagon is a gastrointestinal hormone with a structure and function somewhat similar to secretin. Glucagon has been shown to alter gallbladder function, insulin release as well as gastric motility and secretion. In addition, glucagon has been reported to stimulate pancreatic exocrine secretion,[1, 2] inhibit pancreatic exocrine secretion[3-6] or have no effect on pancreatic exocrine secretion.[7]

The early reports that this hormone inhibited secretion from the exocrine pancreas led to the clinical use of glucagon for the treatment of acute pancreatitis[8, 9] and pancreatic fistulae.[10, 11] Subsequently, the results of treating experimental acute pancreatitis with glucagon have been variable[10, 12] so that few clinicians currently advocate its use in this disease.

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In an attempt to better define the effects of glucagon on the exocrine pancreas, we have reviewed the literature on this subject. This report summarizes the results of this review in terms of histological acinar alterations, exocrine functions in animals, exocrine functions in humans and the effects of this hormone in the treatment of pancreatitis. The possible mechanisms of glucagon activity on the exocrine pancreas are also discussed.

Exocrine Pancreas Histology

The acini, ductules and ducts, all elements of pancreatic exocrine function comprise 98% of the weight of the pancreas. Several studies with light and electron microscopy have shown that the administration of glucagon caused degranulation of these pancreatic acinar cells in experimental animals. The subcutaneous administration of glucagon over a 21-day period to guinea pigs[13] and over a 49-75 day period to rabbits[14] caused degranulation of

the pancreatic acinar cells. In the rat, repeated injections of glucagon caused pancreatic acinar cell degranulation within five hours[15-18] with the appearance of lipid droplets in the cytoplasm.[16-18] This acinar cell degranulation was not prevented by fasting, adrenalectomy, hypophysectomy or atropinization.[15] This effect of repeated administration of glucagon appears to cause an effect similar to splanchnic[19, 20] or vagal[20, 21] stimulation of the pancreas with a discharge of secretory granules from the acinar cells and does not appear to support the idea that a glucagon injection immediately inhibits pancreatic activity. These studies do suggest that the repeated injections of glucagon deplete the zymogen granules of the pancreatic acinar cells and the inactivity or inhibition might be the result of this degranulation.

Animal Pancreatic Exocrine Flow

Glucagon had no immediate effect on the pancreatic exocrine flow, amylase concentration and serum amylase of anesthetized rabbits[22] whose pancreatic duct was cannulated. Five hours after glucagon injection, however, there was a 13% decrease in the amylase concentration in homogenates of pancreas.[22] Glucagon injection decreased pancreatic exocrine volume, bicarbonate, protein concentration, amylase, lipase, trypsin, chymotrypsin[23] and phospholipase A[24] of fasted rats[23, 24] but increased the pancreatic volume, bicarbonate and protein concentration of fed rats.[23] Therefore, while glucagon has little or no effect on the rabbit exocrine pancreas, in the rat its effect on the pancreas might depend on the postabsorptive state and its probable interplay with other hormones.

Pancreatic exocrine flow was measured in one feline preparation with a chronic pancreatic fistula. Glucagon inhibited the pancreatic bicarbonate and protein outputs evoked by exogenous secretin, duodenal acidification or a peptone meal.[25] Pancreatic exocrine secretion was also measured in various canine preparations. In the acute preparation the intravenous[26] and the intra-arterial[26, 27] injection of glucagon increased pancreatic secretion for 10-15 minutes[26-27] then the secretin-stimulated pancreatic exocrine secretion[26] was depressed for 60 to 120 minutes.[26] During the initial increase in pancreatic exocrine secretion, the blood sugar and the A-V blood sugar difference were increased but no such correlation could be found during the reduction in pancreatic exocrine flow.[26] The intravenous infusion of glucose into these dogs did not or only slightly depressed the pancreatic exocrine flow.[26] When a totally isolated pancreas was stimulated with secretin or cholecystokinin, glucagon did not reduce the exocrine volume, amylase, lipase or trypsin concentrations and it was suggested that the inhibitory action of glucagon in the intact animal might be indirect.[1]

Studies were also carried out on chronic dogs with permanent pancreatic fistulas. The intravenous injection of glucagon decreased secretin-stimulated pancratic exocrine flow,[27, 28, 29] sodium, bicarbonate,[28] amylase, lipase, protease and total protein output.[3] The intravenous injection of glucagon also decreased secretin-cholecystokinin-stimulated exocrine flow and total protein concentration but did not alter bicarbonate concentration.[29] The inhibitory effect of glucagon began within five to 15 minutes and lasted 30-45[29] or 60-90 minutes.[3, 28] The intravenous infusion of glucagon depressed the cholecystokinin-stimulated pancreatic protein output[30] and decreased food-stimulated pancreatic exocrine volume, bicarbonate and protein concentration.[4] This inhibitory effect of glucagon appeared almost immediately[4] and the blood glucose was only slightly elevated during the glucagon infusion.[3, 4] Finally,

in a recent study[31] in dogs with chronic gastric and pancreatic fistulae, the duodenum was continuously irrigated with 0.1 N HCl to initiate the endogenous release of secretin. The pancreatic volume and bicarbonate were measured and plasma secretin was determined by radioimmunoassay during and after intravenous infusions of glucagon. It was noted that glucagon depressed the pancreatic volume and bicarbonate without altering plasma secretin levels. This indicated that the glucagon effect is not mediated through the inhibition of secretion release. Therefore, in chronic feline and acute and chronic canine studies, glucagon regularly depresses pancreatic exocrine secretion. This inhibition was not observed, however, in the isolated pancreas preparation, which suggests that glucagon might have an indirect effect on the pancreas.

Human Pancreatic Exocrine Flow

Intravenous injections of glucagon depressed basal pancreatic secretion[5, 32] and amylase output[5] in pancreatic fistula subjects without pancreatic disease[5, 32] while in one study that used duodenal suction in control subjects, glucagon had no effect on the basal amylase or bicarbonate outputs.[33] Intravenous injections of glucagon also reduced secretin-stimulated pancreatic secretion, amylase and protein outputs in pancreatic fistula subjects without pancreatic disease[6] while in one study that used duodenal suction in control subjects, glucagon had no effect on secretin-stimulated pancreatic flow, bicarbonate and amylase outputs.[7] The glucagon did not alter the serum amylase[7, 34] but caused an immediate slight increase in blood glucose[5-7, 33] with no quantitative or temporal correlation with the depressed pancreatic exocrine secretion.[6] Further, intravenous injections of glucagon depressed secretin-cholecystokinin-stimulated pancreatic exocrine flow,[6, 8, 35] bicarbonate,[6, 8] lipase, trypsin, chymotrypsin[36] and total protein[6, 8, 35] in pancreatic fistula patients without pancreatic disease,[6] in a pancreatic fistula patient with a pancreatic cyst[8] and in control subjects that had duodenal suction.[35, 36] In one study in which glucagon depressed the secretin-cholecystokinin stimulated pancreatic enzymes[36] the volume and bicarbonate were not altered. The inhibition of pancreatic exocrine flow by glucagon occurred within five to ten minutes and lasted 10-30 minutes.[35] There was an increase in blood glucose[36] but the blood sugar levels did not follow any pattern.[35] In a study that used duodenal suction in control subjects, intravenous injections of glucagon reduced the effects of endogenous cholecystokinin on the pancreatic trypsin output.[37] Either the glucagon inhibited the stimulatory effects of cholecystokinin or was responsible for inhibiting the release of cholecystokinin from the gut. Finally, the intrajejunal infusion of glucose resulted in elevated serum glucagon levels, a reduced pancreatic volume and bicarbonate with no effect on the pancreatic enzymes in control subjects that had duodenal suction.[38] These studies indicate that, like the animal studies, glucagon depresses pancreatic exocrine secretion. In those few studies[7, 33] in which glucagon did not reduce pancreatic flow, the studies were carried out with duodenal suction which does not always give uniform results.

Pancreatic Disease in Animals

Pancreatitis can be induced in the rat by the injection of olive oil or sodium taurocholate into the pancreatic duct.[24] Neither pretreatment nor treatment with glucagon decreased the mortality rate nor modified the ascites, fat necrosis, pancreatic necrosis, edema or leucocyte infiltration.[24] The induction of pancreatitis in the dog by the technic of the closed-duodenal

loop[9, 10, 39] or by the injection of trypsin and bile salts into the pancreatic ducts[10, 40] resulted in elevated serum glucagon and serum amylase levels.[9, 39, 40] The elevated serum glucagon levels fell within nine hours and the dogs survived about 13 hours.[9, 39] Treatment of the dogs with glucagon increased survival time to about 19 hours[9, 39] while in another study[10] glucagon was not efficacious in treating experimental-induced pancreatitis. Finally, in a recent study,[41] in which pancreatitis was induced in pigs by injection of bile directly into the pancreatic duct after the intravenous injection of secretin, treatment with glucagon modified the course of the disease. The glucagon-treated animals had significant lower serum amylase levels and survived for longer periods of time.

Pancreatic Disease in Man

In patients with acute pancreatitis, it has been reported that the intravenous infusion of glucagon reduced the serum amylase[8, 42, 43] and serum lipase[44, 45] levels, brought relief from pain,[4, 42-45] accounted for clinical improvement[37, 41] and reduced the mortality[42-46] It should be stressed, however, that none of the reports[8, 42-47] made any comparisons with untreated acute pancreatitis patients. It was then of interest when a study[48] was carried out on 26 patients with acute pancreatitis who were randomly assigned to glucagon or placebo treatment. No statistically significant difference was found between the groups as far as pain, nausea, anorexia, abdominal tenderness or serum amylase levels are concerned. This study plus the conflicting observations that during acute pancreatitis the serum glucagon levels may be elevated[49, 50] or depressed[51] certainly questions the efficacy of using glucagon in the treatment of acute pancreatitis.

There is also no definitive evidence for using glucagon in the treatment of chronic pancreatitis. In patients with chronic pancreatitis, intravenous glucagon did not modify the rate, bicarbonate or enzymes of duodenal aspirate following injections of secretin,[7] though in one patient with a pancreatic fistula[8] the basal pancreatic volume was reduced. In addition, no statistically significant difference could be found in the basal serum glucagon levels between control subjects and patients with chronic pancreatitis.[50] Finally, the serum lipase levels and the degree of pain were modified by glucagon in a few cases of chronic pancreatitis but no comparison was made to an untreated group.[44, 45]

Mechanisms of Action

There are probably enough experimental data to concede that glucagon does indeed modify the exocrine pancreas. Glucagon reduces the pancreatic exocrine secretion in both animals and normal human subjects. The mechanism of glucagon action on the exocrine pancreas, however, has not been resolved.

There are a number of possible mechanisms of action of glucagon that might reduce pancreatic exocrine activity. First, glucagon has been observed to reduce pancreatic blood flow[52, 53] but this blood flow reduction has yet to be correlated with a reduced pancreatic exocrine flow. Second, the inhibitory action of glucagon on food-evoked pancreatic secretion may be attributed at least in part to the decrease of gastric acid secretion[54] with subsequent reduction of the release of intestinal hormones by the meal itself. Third, glucagon causes an increase in calcitonin release which results in a lowered serum calcium[40, 55, 56] and phosphate [56] levels with a concomitant hyperglycemia[3, 42, 56] and an increase in the intracellular concentration of adenosine 3′5′-monophosphate.[57] Since calcium is required for amylase secretion by pancreatic slices[58] one might speculate that the hypo-

calcemia caused by glucagon may play some role in the inhibition of pancreatic enzyme secretion. Glucagon might also change the cell permeability for calcium, resulting in intracellular calcium deficiency which would also inhibit enzyme secretion. This theory, however, advocates a direct action of glucagon on the pancreas and does not take into account the possible suggested indirect action[1] of glucagon. Fourth, there is a structural similarity between glucagon and secretin[30, 53, 59, 60] and there might be a competitive-type action between these two hormones. This hypothesis is in contradiction with the data that glucagon depresses canine pancreatic volume and bicarbonate without altering the plasma secretin levels[35] and with the data that glucagon causes pancreatic acinar cell degranulation[13-18] something that does not occur after injections of secretin. Fifth, it has been reported[3, 5, 39, 55, 61] that injections of glucagon can cause hyperglycemia and it was therefore suggested that these elevated serum glucose levels might be responsible for the inhibition of pancreatic exocrine secretion. In rabbits and cats, however, elevated blood glucose levels did not depress lipase concentrations[65] while in dogs the exogenous-stimulated pancreatic secretion was reduced and the endogenous-stimulated pancreatic secretion was not altered.[63] In addition, the intravenous infusions of glucose that raised canine blood sugar levels to 200 mg.% reduced the pancreatic volume by only 10-15%.[23] Blood sugar levels had to be raised above 400 mg.% before 60-70% reductions in pancreatic secretions occurred similar to that observed after intravenous injections of glucagon.[5] In addition, the pancreatic inhibitory effect of glucagon in dogs appears immediately[4] while blood glucose levels were only slightly elevated during the glucagon infusion.[3, 4] In man, elevated blood glucose levels can cause some depression of pancreatic volume[64, 65] and amylase concentration.[65] Glucagon, which caused an immediate slight increase in human blood glucose,[5-7, 37] demonstrated no quantitative or temporal correlation with the depressed pancreatic exocrine secretion.[6] Therefore, in all probability, the inhibiting action of glucagon on the exocrine pancreas does not have to involve blood glucose levels. Sixth, it has been demonstrated that repeated injections of glucagon deplete the zymogen granules of the pancreatic acinar cells[13-18] and the reduced activity might be the result of this degranulation.

The action of glucagon on diseased pancreas has yet to be resolved but there are some interesting experimental data that should be re-evaluated. In recent animal experiments, glucagon appears to increase the survival of dogs[9, 39] and pigs[41] subjected to pancreatitis. Since glucagon infusions can cause degranulation of the pancreatic acinar cells in the guinea pig,[13] the rabbit and the rat,[15-18] glucagon might be putting the exocrine pancreas into an inactive state. At the present time, the effect of glucagon on the diseased pancreas in man is questionable. There are some studies that claim that glucagon has some beneficial effects in the treatment of acute pancreatitis,[8, 42-45] unfortunately no comparisons were made with untreated groups. In the one study[48] in which a comparison was made between a glucagon-treated group and a placebo-treated group, no significant differences were observed. There is also little evidence to support the use of glucagon in the treatment of chronic pancreatitis and the few data that were presented were not compared with untreated groups.

Finally, most investigators seemed to have ignored the fact that there are two types of glucagon. Intrajejunal glucose promotes the release of a glucagon-like substance from the gut.[66, 67] This substance, extractable from the jejunum, is not identical with pancreatic glucagon but is a

larger molecule with distinct biological properties.[66] Both the intravenous infusion of pancreatic glucagon and the intrajejunal infusion of glucose suppress pancreatic secretory flow but pancreatic glucagon produces a suppression of enzyme output with little influence on bicarbonate concentration,[29, 35] whereas intrajejunal glucose results in a significant suppression of bicarbonate concentration with little or no influence on the enzyme concentration.[54] Pancreatic and gut glucagon, each exert an independent suppressive effect on pancreatic exocrine flow but together their inhibitory effect might be powerful enough to alter the course of a diseased pancreas.

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The Parotid and the Pancreas

IV. Parotid Secretion After Secretin Stimulation as a Screening Test of Pancreatic Dysfunction

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In 1971, Kakizaki, et al reported a direct relationship between experimentally-induced pancreatic disorders and alterations of histology and function of the parotid gland.[1] Later the same authors published the preliminary results of the examination of samples of parotid saliva in cases with and without pancreatic disease.[2] They emphasized the usefulness of the saliva test after pilocarpine stimulation as a reliable diagnostic test for diseases of the pancreas.

This is the report of an investigation of salivary and pancreatic secretions obtained simultaneously in patients, after secretin, in order to evaluate the usefulness of such data in the diagnosis of pancreatic disorders.

Technic

Parotid saliva was collected using a "Lashley" saliva cup. This small cup has two holes, the inner one drains the saliva through a thin plastic tube into a graduated test tube; the other hole connects to a rubber insuflater which permits the maintenance of a pressure negative enough to fix the cup to the mucosa and to promote aspiration of saliva. The placement of the cup is easy, depending upon the anatomic location of the opening of Stensen's duct.

The fasting patient is intubated under fluoroscopic control with a Dreiling tube for the secretin test following the technic previously published.[3] The salivary cup is positioned with the patient recumbent. After a basal collection of both salivary and duodenal secretions, 1 U./kg. of secretin "Boots" is injected I.V. and collection of secretions continues for 80 minutes divided into four periods of 10 minutes and two periods of 20 minutes each.

The parameters studied were the same for the pancreas and the parotid gland: 1. Volume of fluid secreted (ml.). 2. Bicarbonate concentration and secretion (mEq.). 3. Protein concentration and secretion (mg.%).

Forty-seven cases were studied as follows: Normal subjects (10 cases); acute pancreatitis (6 cases); nonalcoholic pancreatitis (6 cases); chronic alcoholic pancreatitis (6 cases); alcoholics with pancreatic hypersecretion (6 cases); alcoholics with normal pancreatic function (7 cases); pancreatic cancer (6 cases).

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Results

In patients without pancreatic disease (Table I), the administration of secretin was followed by increased salivary flow in 67% of cases. The mean output increased from 0.2 ml./min. (basal) to 0.3 ml./min. The bicarbonate concentration was also increased in 80% of the patients, the basal average bicarbonate concentration rising from 16-22 mEq./l. The maximum bicarbonate concentration occurred at various times during the test. The salivary maximum bicarbonate, thus, could not be related to salivary flow or to pancreatic maximum bicarbonate. The maximal protein concentration increased but mean protein concentration was similar or even lower than basal values.

In patients with acute pancreatitis (Table II), the basal secretion was higher than in normal patients. After secretin the salivary flow and bicarbonate concentration were less than observed in normal subjects. These tests were performed in patients three to six months after an attack of acute pancreatitis. In all, the pancreatic secretion was still abnormal.

In patients with nonalcoholic chronic pancreatitis, a decrease in salivary flow following secretin was observed. The bicarbonate response did not differ from normal patients. The most striking alterations in salivary findings were observed in chronic alcoholics. These cases were divided in three groups according to the pancreatic function: normal function, hypersecretion and pancreatic insufficiency. In the first group, although a normal basal secretion for volumes and bicarbonates was obtained, a decrease in both parameters, especially for volumes, after secretin stimulation, was observed. The basal secretion was also normal in hypersecretors but after secretin stimulation the volumes and the maximal bicarbonate concentration increased to

TABLE I

Parotid Secretion Before and After 1U./kg. of Secretin in 10 Normal Subjects

Parotid secretion after secretin stimulation

Normal subjects

	Volumes		Bicarbonates			Proteins		
				Postsecretin			Postsecretin	
	Basal ml./min.	Postsecretin ml./min.	Basal mEq./l.	mEq./l. max.	mEq./l. mean	Basal mg.%	(Max) mg.%	(Mean) mg.%
Mean	0.2	0.3	17	22	17.8	158.5	185.8	153.8
Observed range	0-0.4	0.15-0.85	16-27	18-27	13-25	100-239	156-223	104-210

TABLE II

PAROTID SECRETION BEFORE AND AFTER 1U./KG. OF SECRETIN IN NORMALS AND IN PANCREATIC DISEASES

Parotid secretion after secretin stimulation in pancreatic disease (means)

	No.	Volumes			Bicarbonates			Proteins mg.%
		Basal ml./min.	Postsecretin		Basal mEq./l.	Postsecretin		
			ml./min.	ml./hr.		mEq./l. max.	mEq./l. mean	
Normal	10	0.2	0.3	12.6	17	22	17.8	153.8
Alcoholics								
Normal pancreas	7	0.3+	0.17	9.8	16	19.7	13.3	226
Hypersecretors	6	0.2	0.24	11.9	16	20.2	14.8	177
Insufficiency	6	0.06	0.16	8.9	8	10.8	7.8	145
Chronic pancreatit.s (nonalcoholic)	6	0.15	0.13	8.3	18	19.6	14.6	208
Acute pancreatitis	6	0.38	0.22	11.3	20	15	11.0	140

values similar to those observed in normals. Finally, in the patients with pancreatic insufficiency, the salivary flow and bicarbonate content, before and after secretin, were markedly less than in the normal subjects. The protein content of saliva in alcoholics with normal pancreatic function was observed to be higher following secretin stimulation than in normal subjects. In alcoholics protein concentration and protein output following secretin appeared to decline in parallel fashion with pancreatic secretion. In nonalcoholic chronic pancreatitis, the postsecretin mean protein concentration was higher than in normal subjects. Two cases of parotid hypersecretion were observed in heavy drinkers, one with normal pancreatic function and one with pancreatic hypersecretion (Table III).

In patients with pancreatic cancer, postsecretin salivary flow was either in the normal range or completely suppressed. Absent salivary response to secretin was observed most frequently in the advanced cases.

COMMENT

Although the data are difficult to interpret some generalizations appear warranted from the observations. 1. Pancreatic pathology appears to be associated with decreased salivary flow after secretin. 2. Only in patients with chronic alcoholic pancreatitis were significant changes in the salivary bicarbonate response to secretin noted. 3. Basal salivary flow is depressed in non-alcoholic as well as alcoholic pancreatitis. 4. The salivary response to secretin in patients with alcoholic pancreatic insufficiency shows depressed flow, bicarbonate, and protein.

One can only speculate as to the origin of these salivary secretory alterations. The possibilities include: 1. Injury to the parotid by the agent noxious to the pancreas. 2. In-

TABLE III

TWO CASES OF CHRONIC ALCOHOLISM WITH HIGH PAROTID SECRETION (PAROTID HYPERSECRETION)

	Volumes		Bicarbonates	
	Basal	Postsecretin	Basal	Postsecretin
Case 2/77	0.8 ml./min.	20.6 ml./hr.	27 mEq./l.	57 mEq./l.
Case 19/77	0.34 ml./min.	24.3 ml./hr.	21 mEq./l.	35 mEq./l.
Normals	0.2 ml./min. (0.-0.4)	12.6 ml./hr. (7.3-27.8)	17 mEq./l. (16-27)	22 mEq./l. (18-27)

hibition of the parotid by a substance secreted into the bloodstream by the diseased pancreas, perhaps a hormonal inhibitory factor similar to myocardial depressant factor. 3. Decreased parotid responsiveness to feedback mechanisms initiated by the injured pancreas. It may very well be that one or more of these hypotheses is operative in the different pathologies.

The data definitely indicate the possibility of hormonal as well as neural regulation of salivary flow. At this point, however, it is difficult to establish criteria whereby pancreatic disease can be reliably diagnosed on the basis of salivary secretory responses to secretin.

CONCLUSIONS

The parotid is responsive to secretin stimulation in man.

The pattern of secretion of the parotid appears altered in patients with pancreatic disease with some parallelism between the salivary and pancreatic responses to secretin.

On the basis of the data it appears questionable whether the physiologic phenomenon described will be clinically useful in the diagnosis of pancreatic disease.

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Communication from Abroad

Long-term Treatment with Histamine H_2-receptor Antagonists in Zollinger-Ellison Syndrome

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Continuous treatment of three Zollinger-Ellison patients with histamine H_2-receptor antagonists for 14, 26 and 31 months resulted in effective relief of complaints and marked reduction in gastric acid secretion. In one of the patients the dose of cimetidine had to be doubled after 15 months of treatment because of a rise in basal gastric acid secretion accompanied by recurrent diarrhea. Fasting and secretin-stimulated serum gastrin levels were not affected by long-term treatment with histamine H_2-receptor antagonists. No side-effects were observed in the three patients on long-term treatment.

Introduction

Histamine H_2-receptor antagonists have proved to be potent inhibitors of pentagastrin-stimulated gastric acid secretion.[1] These drugs have therefore been used in the treatment of hypersecretion of gastric acid in patients with the Zollinger-Ellison syndrome.[2-8]

Reports on long-term efficacy of H_2-receptor antagonists, however, are conflicting.[9, 10] Bonfils, et al[9] found partial reduction in efficacy in one and total inefficacy in five out of ten cases with Zollinger-Ellison syndrome treated for 15-190 days. McCarthy, et al,[10] on the other hand, found histamine H_2-receptor blocking agents effective in all seven Zollinger-Ellison patients treated for one to 15 months.

In this study we report on the effect of long-term treatment with histamine H_2-receptor antagonists on basal gastric acid secretion, fasting and secretin-stimulated serum gastrin concentrations and clinical symptoms in three Zollinger-Ellison patients during continuous treatment for 14, 26 and 31 months.

Patients and Methods

In all three patients the diagnosis of Zollinger-Ellison syndrome was based upon basal gastric hypersecretion (12-67 mmol/hr.), fasting hypergastrinemia (340-595 pg./ml.), serum gastrin responses of at least 50% of basal value both to calcium, 15 mg./kg./3 hr. and to secretin GIH (GIH Laboratories, Karolinska Institutet, Stockholm, Sweden), 1 C.U./kg./30 sec and postprandial increases in serum gastrin of less than 50% of basal level (Fig. 1 and Table I). All three patients originated from families with multiple endocrine adenomatosis type I.

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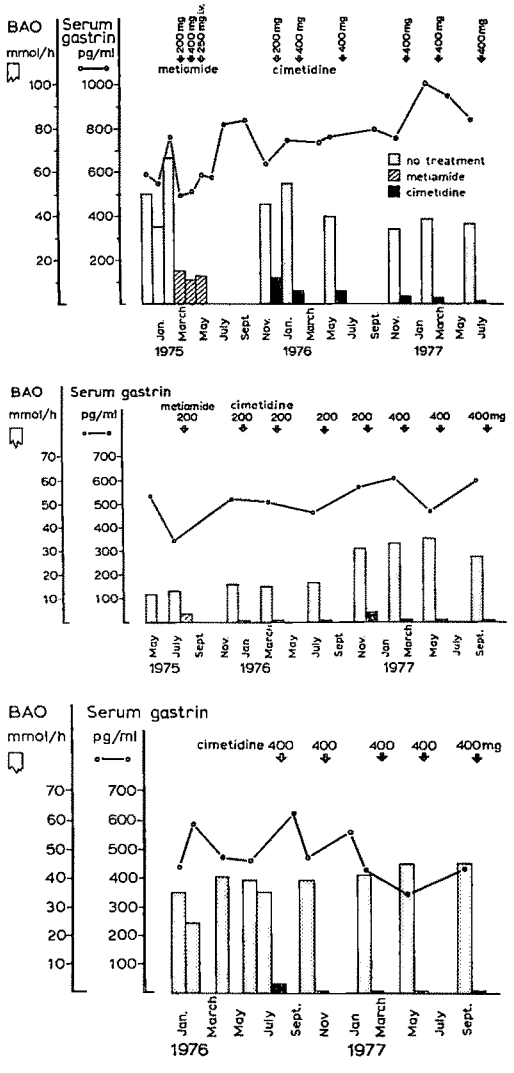


Fig. 1—The effect of long-term treatment with histamine H_2-receptor antagonists on basal gastric acid secretion and serum gastrin in three patients with Zollinger-Ellison syndrome. The upper diagram represents Case 1, the middle, Case 2 and the lower, Case 3.

Case Report

Case 1:—A 40-year old man had suffered from diarrhea and weight loss since 1965. In 1974 a diagnosis of Zollinger-Ellison syndrome and presumptive hyperparathyroidism was made. From January, 1974 to March, 1975 the patient was treated with high doses of anticholinergic drugs resulting in only moderate relief of diarrhea. In March, 1975 a treatment with metiamide was started.

Case 2:—A 39-year old woman had three pancreatic β-islet cell tumors resected in 1954. In 1968 three hyperplastic parathyroid glands were resected for hyperparathyroidism. Since 1967 she had suffered from recurrent duodenal ulcers and diarrhea. In 1975 a diagnosis of Zollinger-Ellison syndrome was made. Treatment with metiamide was started in August, 1975. At that time the patient had diarrhea but no active duodenal ulcer.

Case 3:—A 38-year old woman had suffered from gastric pain, heartburn, diarrhea and weight loss since 1972. In 1975 a diagnosis of Zollinger-Ellison syndrome and presumptive hyperparathyroidism was made. From March, 1976 to August, 1976 she was treated with high doses of anticholinergic drugs resulting in only moderate relief of complaints. In August, 1976 treatment with cimetidine was started. At that time the patient had severe diarrhea and an active postbulbar ulcer.

Gastric aspiration was performed as described by Hector.[11] Gastric acid was determined by titration of gastric juice with 0.1 N NaOH up to pH 7.0. The basal gastric acid output was measured after discontinuing the drug for 36 hours and also between one and two hours after the oral intake of the histamine H_2-receptor antagonist. In Case 1 the basal gastric acid secretion was also measured during intravenous infusion of metiamide (Fig. 1).

Serum gastrin concentrations were measured by radioimmunoassay.[12] Venous blood was drawn after an overnight fast, immediately before gastric intubation or the ingestion of the drug. Serum gastrin levels using this assay were 66 ± 18 (S.D.)

TABLE I

EFFECT OF LONG-TERM TREATMENT WITH HISTAMINE H_2-RECEPTOR ANTAGONISTS ON FASTING AND SECRETIN-STIMULATED SERUM GASTRIN LEVELS IN THREE PATIENTS WITH ZOLLINGER-ELLISON SYNDROME

Case	Date	Treatment	Serum gastrin (pg./ml.)			
			0	+ 5 min.	+ 10 min.	+ 15 min.
1	1/6/75	–	595	1,300	990	760
	8/27/75	Metiamide 400 mg.	810	1,680	1,450	1,150
	11/19/76	Cimetidine 400 mg.	755	1,450	1,015	875
	6/27/77	Cimetidine 400 mg.	820	1,630	1,310	890
2	8/12/75	–	340	910	715	530
	9/9/75	Metiamide 200 mg.	340	1,440	990	740
	5/11/77	Cimetidine 400 mg.	330	1,450	1,040	770
3	7/25/75	–	440	990	820	630
	5/13/77	Cimetidine 400 mg.	330	1,010	890	590

Secretin (GIH-Laboratories, Karolinska Institutet, Stockholm, Sweden) in a dose of 1 C.U. kg./30 sec., was administered intravenously at time 0, corresponding to 2 hours after the oral intake of the drug.

pg./ml. in 100 normal controls and 70 ± 20 pg./ml. in 80 duodenal ulcer patients. Blood, liver and kidney toxicity tests were done biweekly in metiamide and every four weeks in cimetidine treated patients.

RESULTS

Case 1 was treated with 1.0 gm. of metiamide daily, 0.2 gm. after meals and 0.4 gm. at bedtime from March, 1975. In May, 1975 the dose was increased to 2.0 gm. daily, 0.4 gm. after meals, at bedtime and at midnight, because of a poor clinical response. This latter dose led to a marked relief of diarrhea, a decrease in fecal fat excretion from 32-15 gm. daily and a weight gain of 4 kg. within five months. From October, 1975 he suffered from recurrent attacks of abdominal pain with raised levels of amylase in blood and urine and a diagnosis of pancreatitis and gallstones was made. In November, 1975 metiamide was replaced by cimetidine in the same dosage. In February, 1976 liver tests showed partial biliary tract obstruction and at laparotomy an expanded gallbladder containing multiple small gallstones and an enlarged, nodular and firm pancreas were found. Choledochoduodenostomy and cholecystectomy were performed. A biopsy from the pancreatic body confirmed the diagnosis of pancreatitis but failed to reveal tumor lesions. About three months after surgery the patient developed overt pancreatic insufficiency and diabetes mellitus. Replacement therapy with pancreatic extract and insulin was started. At present, the patient is in a reasonable general condition without pain but with moderate diarrhea and steatorrhea of about 15 gm. daily. The basal gastric acid output, both without and with histamine H_2-receptor antagonists and the fasting serum gastrin levels are shown in Figure 1.

Case 2 was treated from August, 1975 to November, 1975 with 0.8 gm. of meti-

amide daily, 0.2 gm. after meals and at bedtime. From November, 1975 to November, 1976 she received 0.8 gm. of cimetidine daily, resulting in complete disappearance of diarrhea, a decrease in fecal fat excretion from 12-6 gm. daily and a weight gain of 2 kg. In November, 1976 she experienced recurrence of diarrhea. Basal gastric acid output, both without and with cimetidine, was found to be higher than previously (Fig. 1). For that reason the dose of cimetidine was increased up to 1.6 gm. daily, 0.4 gm. after meals and at bedtime, resulting in a complete disappearance of diarrhea.

Case 3 was treated from August, 1976 with 1.0 gm. of cimetidine daily, 0.4 gm. after breakfast and 0.2 gm. after lunch, after dinner and at bedtime. This treatment resulted in marked relief of complaints, healing of the postbulbar ulcer after six weeks, a decrease in fecal fat excretion from 17-7 gm. daily and a weight gain of 7 kg. within 10 months. Results of basal acid secretion, with and without histamine H_2-receptor antagonists and fasting serum gastrin levels are shown in Figure 1.

The results of the gastrin responses to secretin GIH 1 C.U./kg./30 sec., before and during treatment with H_2-receptor antagonists are presented in Table I.

Repeated laboratory tests did not show any hematological, renal or liver toxicity. None of the patients had gynecomastia, galactorrhea or elevated serum prolactin levels (less than 14 ng./ml.; normal value less than 20 ng./ml.) Detailed study of the cellular and humoral immunology (mixed lymphocyte culture, skin tests, autoantibody production and serum immunoglobulin concentration) in Cases 1 and 2 after treatment with histamine H_2-receptor antagonists for 25 and 20 months respectively, revealed no abnormalities.[13]

Comment

This study shows that histamine H_2 receptor antagonists are able to inhibit gastric acid secretion in Zollinger-Ellison patients for periods up to two and a half years. In one patient (Case 2) the dose of cimetidine had to be increased in order to maintain adequate inhibition of gastric acid secretion. This was not attributable to a reduction in efficacy but was found to be related to a rise in basal gastric acid output. Since fasting serum gastrin levels did not greatly change in this patient, an increased sensitivity of the parietal cells to gastrin might have been involved in the rise in gastric acid secretion. Although no hard evidence for this suggestion is presented, it is supported by the finding that administration of metiamide to rats is ineffective in blocking pentagastrin-stimulated DNA-synthesis by the gastric mucosa.[14]

Basal gastric acid secretion did not markedly change in Cases 1 and 3 and histamine H_2-receptor antagonists were found to be effective in a more or less dose-dependent manner. Our results contrast with those of Bonfils, et al,[9] who found partial reduction in efficacy in one and total ineffi-cacy in five cases during administration of histamine H_2-receptor antagonists for 15-190 days. Furthermore, we did not observe a so-called "prolonged inhibition" of gastric acid secretion after withdrawal of metiamide or cimetidine.[15] Within 12 hours after withdrawal of the drug all three patients experienced a recurrence of diarrhea and gastric acid secretion was not found to be markedly reduced 36 hours after discontinuing the drug.

Bonfils, et al[9] also found that secretin was no longer capable of increasing serum gastrin levels in two out of five Zollinger-Ellison patients on treatment with histamine H_2-receptor antagonists. In our three Zollinger-Ellison patients on long-term

treatment, neither the fasting serum gastrin level nor the serum gastrin response to secretin changed markedly (Table I).

The clinical efficacy of the histamine H_2-receptor antagonists was excellent in Cases 2 and 3. The efficacy of cimetidine in Case 1 was difficult to assess since this patient had concomitant pancreatic insufficiency. Metiamide was clinically effective, however, before the onset of pancreatitis and also during pancreatic insufficiency cimetidine markedly reduced diarrhea in this patient. Although the diagnosis of pancreatitis was made during treatment with histamine H_2-receptor antagonists, we do not believe that this disorder was related to the drugs used. Co-existing abnormalities, such as hyperparathyroidism or pancreatic tumors, might have been involved in the pathogenesis of pancreatitis in this patient. Moreover, serum and urinary levels of amylase were repeatedly normal in the two other Zollinger-Ellison patients on long-term treatment.

None of our patients had gynecomastia, galactorrhea or increased serum prolactin concentrations, as have been found by others.[16-18] No adverse reactions of an immunological nature, as suggested previously,[19] could be demonstrated by detailed immunological studies.

In conclusion, histamine H_2-receptor antagonists were effective in the long-term symptomatic treatment of our Zollinger-Ellison patients, without side-effects. Although it is clear that more patients have to be studied for longer periods, our results show that long-term treatment with histamine H_2-receptor antagonists may be a valuable alternative therapy for total gastrectomy in the Zollinger-Ellison syndrome.

Addendum

At present, (September, 1978) cimetidine is still effective in all three cases.

Acknowledgments

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Clinical Vignette

Primary Aortoduodenal Fistula

Case Presentation and Review of Literature

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One hundred and twelve cases of primary aortoduodenal fistulas were reviewed. The most common etiological agent was an atherosclerotic infrarenal abdominal aortic aneurysm. There was a male to female predominance of 9:2 with an average age of 62 years. Most fistulas occurred between an infrarenal aneurysm and the third portion of the duodenum because of the relatively fixed position of the duodenum and its direct anatomical relationship posteriorly with the aorta. Patient symptoms may vary from abdominal or back pain with gastrointestinal bleeding to just hematemesis or melena. Twenty per cent gave a history of abdominal aneurysm while up to 70% may have an abdominal mass on physical examination at the time of admission. Tentative diagnosis is established by history and physical examination with duodenoscopy, barium duodenogram and angiography available only if temporally feasible. Surgical exploration is the only treatment with resection of the aneurysm, synthetic graft placement and duodenal suturing as the procedure of choice.

Introduction

Primary aortoduodenal fistulization is a rare and usually fatal condition. Its incidence is considerably less than fistula secondary to reconstructive aortic surgery. Preservation of the life of a patient requires prompt diagnosis coupled with adequate surgical intervention. The advent of synthetic grafts has made operative repair feasible, with the major faults being in failure to recognize this disease entity as a source of gastrointestinal bleeding.

This paper describes one case in which the diagnosis was made intraoperatively and reviews and analyzes the literature of this disease.

Case Report

A 59-year old black male was admitted to the Bronx Veterans Administration Hospital for a second attempt at excision of a sphenoid ridge meningioma. A previous craniotomy at another hospital revealed a 5 cm. unresectable tumor. This first surgery was followed by a course of extensive radiotherapy. The patient's symptomatology remained unchanged for the following one and a half years until he began to experi-

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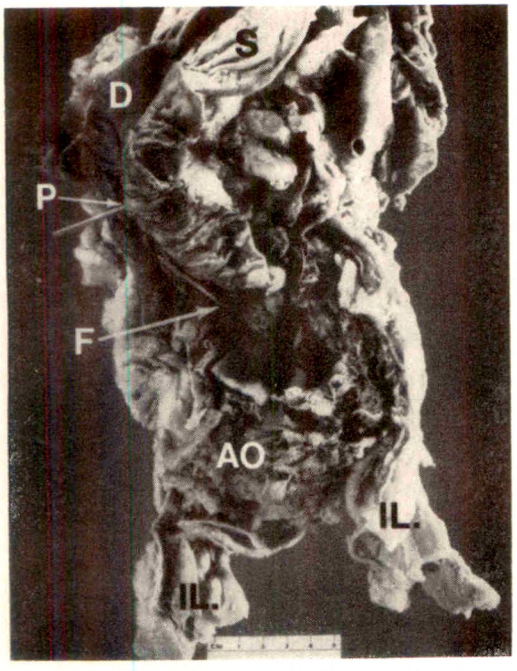


Fig. 1—Anterior view of fixed specimen.

S — Stomach
D — Duodenum
P — Papilla of Vater
F — Fistula
Ao — Aorta
Il — Iliac arteries

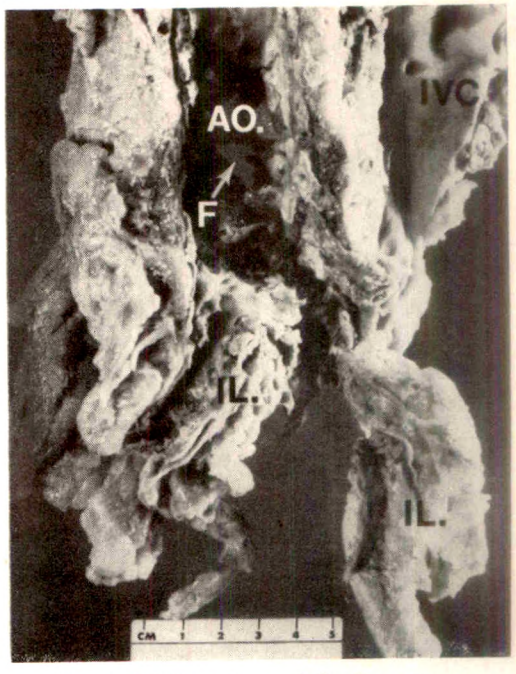


Fig. 2—Posterior view of fixed specimen.

Ao — Aorta
F — Fistula
IVC — Inferior vena cava
Il — Iliac arteries

ence progressive deterioration of mental functions. On this hospital admission, he showed general retardation of mental functions and slow verbal responses. The patient's past medical history was unremarkable except for vague epigastric pains experienced five years ago and relieved by antacids. There was never any documentation of peptic ulcer disease, diabetes mellitus or hypertension. The patient smoked one pack of cigarettes per day since he was a teenager. There was no history of claudication, impotence, back or testicular pain. Physical examination demonstrated a well developed moderately obese male with no palpable abdominal masses or organs, equal and normal pulses bilaterally and no peripheral arterial bruits. The patient's medications were phenolbarbitol and Decadron.

Four weeks after admission to this hospital the patient experienced a bowel movement of clotted blood. He was alert and responsive with stable blood pressure and pulse rate. Nasogastric intubation revealed mild active bleeding with coffee grounds. This rapidly cleared after ice water lavage. Hematocrit fell from 42-32% after hydration. Endoscopy was performed and this revealed a large clot with mild oozing high on the greater curvature. The second to third portion of the duodenum demonstrated a reddish, raised, plaque like area. No ulcer or bleeding at this level was seen. The patient did well over the next six hours until a massive gastrointestinal hemorrhage necessitated emergency laparotomy. At the time of surgery a 2 cm. aortoduodenal fistula, secondary to an atherosclerotic infrarenal abdominal aneurysm, was found. Attempt at repair was un-

TABLE I

LOCATION OF PRIMARY AORTODUODENAL FISTULA

Duodenal location	Number	Percent
First portion	1	0.9
Second portion	5	4.5
Third portion	80	71.4
Fourth portion	7	6.2
Unspecified	19	17.0
Total	112	100.0

TABLE II

AGE AND SEX DISTRIBUTION OF 112 PATIENTS WITH PRIMARY AORTODUODENAL FISTULA

	Number of cases*	Per cent of cases	Average age
Male	90	82	62 yr.
Female	20	18	61 yr.

* Unknown = 2 cases

TABLE III

ETIOLOGY OF SPONTANEOUS PRIMARY AORTODUODENAL FISTULA

Etiology*	Number of cases		Average age	
	Male	Female	Male	Female
Atherosclerotic	73	16	66	64
Syphilitic	7	0	40	—
Mycotic	2	1	41	20
Traumatic	1	0	18	—
2° to pancreatic carcinoma	0	1	—	55
Tuberculosis	1	—	70	—

* Unknown = 10 cases

TABLE IV

PRESENTING SYMPTOMS OF 112 PATIENTS WITH PRIMARY AORTODUODENAL FISTULA

Symptom	Number	Per cent
Hematemesis	73	65
Melena	61	55
Abdominal pain	52	46

successful and the patient expired. Postmortem examination revealed a 2 cm. primary aortoduodenal fistula (Figs. 1 and 2).

COMMENT

In 1829 Sir Astley Cooper[1] first described a case of aortoenteric fistulization. It was not until 1956 when Polk, Martinay and DeCastro[2] and Voyles and Mortez[3] attempted surgical repairs. In 1961 Maclean and Couves[4] performed the first successful operation using the technic of resection and graft. One hundred and twelve patients[1-23] with primary aortoduodenal fistula, including the case described, have been reported in the literature. There have been a few even rarer cases of aortocaval[22] and aorta to stomach, small or large bowel fistulization[14, 15] Reckless[14] lists 24 cases of aortoenteric fistula, excluding those to the duodenum, giving the duodenum an almost 5:1 predominance. This can best be explained on an anatomical basis. The duodenum is the shortest, widest and most fixed portion of the gastrointestinal tract. Its third portion is covered anteriorly by peritoneum but rests posteriorly on the aorta just distal to the origin of the renal arteries. It is because of this relatively fixed retroperitoneal position with direct apposition to the aorta that this segment has the greatest incidence of fistulization (Table I). Seventy-one per cent of the aortoduodenal fistulas rupture into the third portion of the duodenum.

Age and sex distribution are listed in Table II. Eighty-two per cent of all cases

TABLE V

SURVIVAL OF PATIENTS WITH PRIMARY AORTODUODENAL FISTULA

	Number	Percentage
Surgically treated	33	29
Operative survival	15	45
Operative mortality	18	55
Over all survival	15	13
Over all mortality	97	87
Total cases	112	100

TABLE VI

OPERATIVE PROCEDURES EMPLOYED IN THE TREATMENT OF PRIMARY AORTODUODENAL FISTULA

Operative technic	Number	Survival	% Survival
Laparotomy alone	6	0	0
Transduodenal repair of fistula	3	0	0
Primary suture of duodenum and aorta	4	2	50
Resection and tube or bifurcated synthetic graft	20	12	60

occur in males with an average age in both sexes being between 61 and 62 years.

Etiological factors, predisposing to this problem, are arteriosclerosis, syphilis, mycosis, tuberculosis, trauma and carcinoma (Table III). Anti-tuberculous, fungal and syphilitic drugs have made these causes so rare that no cases have been reported in over 30 years. The exact mechanism of aortoduodenal fistulization remains obscure. Shromak[15] lists four factors influencing this rupture as: 1. hemodynamic, 2. degenerative, 3. infectious agents and 4. any combination of these three factors. To these should be added anatomical relationships and inflammatory processes. As the aortic aneurysm forms by destruction of elastic fibers of the aortic wall, with subsequent fibrosis, an inflammatory tissue reaction occurs around this area. The anatomical relationships between the third portion of the duodenum and the aorta cause these two structures to adhere to each other. This inflammatory tissue reaction between aorta and contiguous bowel and the constant direct pulsations may together cause vascular compromise and ultimate duodenal necrosis resulting in fistulization. Hemorrhage has been demonstrated by the presence of hemosiderin in the connective tissue spaces between aneurysm and gut,[13] supporting this theory.

Symptoms include all of those typical of aortic aneurysm such as abdominal fullness, back pain, abdominal pain or pain radiation to the hip, scrotum or inner aspect of the thigh. Twenty per cent[14] of the patients are aware of an abdominal mass. In addition 65% will complain of hematemesis and 55% of melena (Table IV). Physical examination reveals an abdominal mass between 56%[14] and 70%[3] of the time. Evidence of recent gastrointestinal bleeding may or may not be present. The time interval from initial bleeding to fulminant hemorrhage is quite variable. Voyles[3] and Reckless[14] agree that only 27% present with bleeding of less than six hours and that 59% have a history of hemorrhaging for more than 24 hours. This may be explained by the presence of laminated clots within the aneurysmal wall causing occlusion of the defect. This may then intermittently bleed until such time as further duodenal destruction occurs or until clot is dislodged

resulting in rapid exsanguination. This delay before the first symptoms and the patient's death may offer adequate time for surgical correction.

The only successful treatment of primary aortoduodenal fistula is surgical intervention. Patients are often believed to have peptic ulcer disease or diverticulosis. Kirk, et al[23] believe that peptic ulcer disease may be three times higher in patients with abdominal atherosclerotic aneurysm. The age of the patients, presenting symptoms, physical examination and rarity of aortoduodenal fistula are the cause of misdiagnosis and thus poor prognosis. Survival statistics are listed in Table V. Only 29% of all cases were surgically treated with an operative survival of 45%. This gives an over all mortality of 87%. The operative statistics would be greatly improved if there was a correct preoperative diagnosis. The various operative technics employed are listed in Table VI. Resection and grafting as the presenting symptoms of carcicure rate and survival of 60%. In establishing the correct diagnosis one must suspect this entity. Any patient with a history of abdominal aneurysm, or palpable abdominal mass with acute gastrointestinal bleeding merits early abdominal exploration. Angiography may demonstrate an aneurysm with fistulization; however, by this time the hemorrhaging may be so extensive as to compromise the patient's survival. Documentation of an aneurysm without demonstration of enteric extravasation does not rule out fistulization. A barium duodenography showing an ulcer in the transverse duodenum[5] in the presence of an aneurysm may be considered highly suggestive[15] as may duodenoscopy showing a plaque-like ulceration distal to the ampulla of Vater. These studies may aid in diagnosis but the presence of an abdominal aneurysm with or without radiographic or endoscopic findings in conjunction with acute gastrointestinal hemorrhage should be sufficient indication for abdominal exploration.

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Clinical Vignette

CT-guided Percutaneous Drainage of an Amebic Liver Abscess

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Computed tomography (CT) has been successfully applied to the diagnosis of abnormalities of the solid abdominal organs. In a patient with liver abscess, CT was used to direct percutaneous drainage of a loculated portion of the abscess. The use of CT for biopsy and treatment of intra-abdominal diseases should become more common as scan time decreases.

Computed tomography (CT) is rapidly assuming great importance as a diagnostic tool in the evaluation of the solid abdominal organs. The ability of CT to accurately localize a pathologic process in three dimensions suggests an important role in this modality in the percutaneous biopsy and treatment of intra-abdominal diseases. First reports of the use of CT for localization and percutaneous technics have recently appeared in the literature.[1-5] We report a case of percutaneous liver abscess drainage with CT localization.

Case Report

A 24-year old black African university student was in good health until 12 days prior to admission, when he began having right shoulder pain, which increased with inspiration and movement of his shoulder. There was no radiation of the pain to the back or across the chest. He then developed a fever which characteristically spiked at about 6 p.m. daily. He was treated at first with aspirin, and then with ampicillin 500 mg. P.O. q.4.h. at his university infirmary. Laboratory data obtained at the university infirmary revealed a WBC of 21,800 with 70 polys. 13 stabs, 13 lymphs, 3 monos and 1 eosinophil. Urinalysis showed a trace of albumin. The patient had lost an unknown amount of weight and had mild fatigue and dyspnea on exertion. The past medical history was significant in that he had had malaria with many recurrences.

Initial physical examination at Scottsdale Memorial Hospital showed a temperature of 39.2° C; blood pressure, 110/70; pulse, 100; respiration, 20. He was in moderate discomfort due to right shoulder pain. Dullness to percussion was elicited in the

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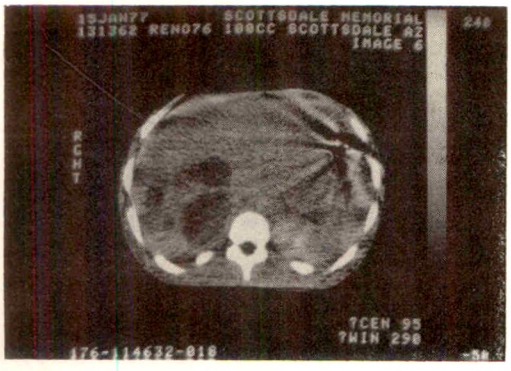


Fig. 1—Admission CT scan shows multiple low density lesions in right lobe of liver posteriorly.

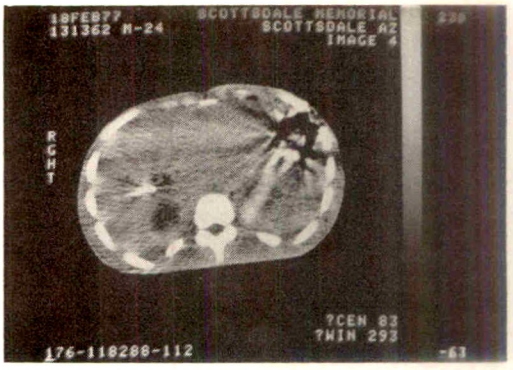


Fig. 3—The high density object is the tip of the surgical drain. A second abscess locule is seen posterior to the drainage site.

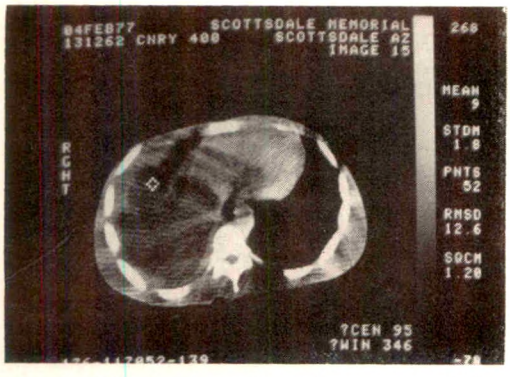


Fig. 2—The abscess cavity is larger on a follow-up examination, involving most of the right lobe of the liver. Electronic cursor shows density of material within abscess cavity to be that of water (between +10 and −10).

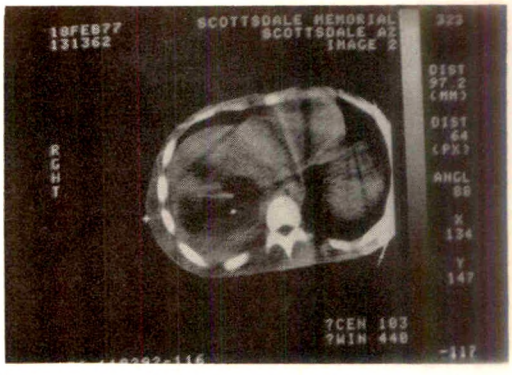


Fig. 4—Tip of percutaneous drainage catheter seen in posterior locule of liver abscess. Electronic measuring device used to measure distance between skin surface and center of the abscess cavity (97.1 mm.).

right lung base. The abdomen was soft, although there was mild tenderness in the right upper quadrant. There was a mass present just to the right of the mid line below the right costal margin, felt to represent an enlarged liver. No splenomegaly was appreciated and the bowel sounds were active. Initial laboratory studies included a WBC of 27,400 with 70 polys, 16 stabs, 12 lymphs and 2 monos. Hemoglobin was 11.9; hematocrit, 34.6; sedimentation rate, 120. The sickle cell prep was negative. Malaria smear showed no malarial parasites. Urine showed a trace of protein, 3+ bile, 3-4 WBC and occasional bacteria. Electrolytes were normal. Creatinine was 1.8 with BUN 19. Bilirubin, 1.8 direct, total 3.0. Stool specimens showed *Ascaris lumbricoides* ova and *Trichuris trichuria* ova. Serum amylase was within normal limits. Amebic titers were obtained and sent to the Communicable Disease Control Laboratory. These were reported as within the range of 1:1024 and 1:2048.

Computed tomography (CT) of the liver on the day after admission showed areas of decreased attenuation most compatible with liver abscesses, amebic abscess being the primary consideration (Fig. 1).

Radionuclide liver scan and ultrasound were also compatible with liver abscess. Chest x-ray revealed no infiltrative process and there was an elevated right hemidiaphragm. Two days after admission a laparotomy was performed. The liver was swollen and three aspirations produced thick, creamy purulent material mixed with blood. This material was cultured for aerobic, anaerobic, acid fast and fungal organisms. All the cultures were negative. A hepatic dainage tube was placed and connected to suction. The temperature remained elevated at 39.6° C and the white count went to 42,000. Gentamycin 80 mg. I.M. q.12.h., Ancef 1 gm. I.V. q.8.h. and clindamycin 80 mg. I.V. q.6.h. were begun. In spite of this vigorous antibiotic therapy the patient remained febrile and the white count remained elevated. On the seventh day following admission antibiotic therapy was discontinued and the patient placed on Flagyl 70 mg. P.O. t.i.d. From that time on his white count continued to fall reaching a level of 13,700 on the 17th day postadmission.

In spite of the patient's general clinical improvement, with decrease in temperature and white count, he continued to complain of right shoulder pain and some right upper quadrant tenderness. Repeat CT scan showed reaccumulation of abscess fluid (Fig. 2). On the 30th postadmission day the patient underwent blind transcutaneous drainage of the liver abscess. A large amount of sanguinopurulent material was obtained and the drainage tube was connected to suction. Repeat cultures of the drainage again revealed no growth. The patient tolerated the procedure well but continued to have intermittent right shoulder pain with the tube in place. A third repeat CT scan again showed abscess, loculated away from the site of tube drainage (Fig. 3). The center of the remaining large abscess cavity was localized as to level and the depth from skin surface to center of abscess determined, using the CT scanner. A #18 gauge Teflon-sheated needle was advanced into the liver to the proper depth, the needle removed and the Teflon sheath left in place (Fig. 4). Approximately 30 cc. of sanguinopurulent material was obtained. Repeat cultures again proved negative. The catheter was connected to suction..

Following this procedure the patient progressed satisfactorily. His white count returned to a normal range, at approximately 8,200. Differential showed 56 polys; 33 lymphs; 5 monos and 6 eosinophils. The patient's appetite gradually increased and he began to put on weight. The abscess drainage tubes were removed on the 36th postadmission day. He was discharged six days later in markedly improved condition and on no medication.

Comment

In the past year, CT has been used to drain abdominal and hepatic abscesses, and to perform antegrade pyelography.[1-5] In this patient, the progress of the multiloculated hepatic abscess was followed with CT and the efficacy of drainage procedures monitored. The use of the scanner to localize the remaining locule of abscess and direct the percutaneous drainage catheter to this abscess, illustrates the ability of the procedure to accurately localize pathology. As the scan time decreases to a level at which the patient can hold respiration, the ability to perform CT directed invasive procedures will increase. This may obviate the need for surgical intervention in some patients with intra-abdominal disease.

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Clinical Vignette

Giant Cell Carcinoma of the Pancreas

Report of a Case with Upper Gastrointestinal Bleeding Diagnosed by Endoscopic Brush Cytology

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A case of upper gastrointestinal bleeding as the first and only manifestation of giant cell carcinoma of the pancreas invading the duodenum is described. The polypoid tumor was visualized during endoscopy. The diagnosis was made by a cytologic brush and confirmed by endoscopic biopsy. The rather uncommon presentation of pancreatic carcinoma and the possibility of establishing the diagnosis by a cytologic brush is discussed.

The course and prognosis of carcinoma of the pancreas did not change in the last 30 years,[1] partly because it usually escapes early diagnosis.[1, 2] The durations of symptoms prior to admission to hospital averages six to seven months.[1, 3] A high degree of suspicion seems to be the key for early diagnosis.

The diagnosis is delayed mainly because the initial symptoms are often vague and ill defined. The triad, typical of pancreatic carcinoma—weight loss, abdominal pain and jaundice—appears usually late in the course of the disease and is not always present. Bleeding from the upper gastrointestinal tract can be caused by this tumor but usually it is a late manifestation.[4]

A case in which the only and presenting manifestation of pancreatic carcinoma was upper gastrointestinal bleeding is presented. Moreover, to our knowledge this is the first reported case in which endoscopic examination with direct vision cytologic brushings provided the diagnosis of the tumor.

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Case Report

A 73-year old white woman was admitted to the hospital because of melena in the three weeks prior to her admission. Her past history included pulmonary tuberculosis and ulcer disease, manifested by epigastric pain and melena 40 years and three years previously. The patient denied abdominal pain, heartburn or weight loss. She had no history of drug intake, smoking or drinking alcohol. Barium meal, one week prior to the admission, revealed a deformity of the duodenal bulb, compatible with duodenal ulcer.

On examination, her pulse was 84/min. and B.P. 180/80 mm. Hg. The abdomen

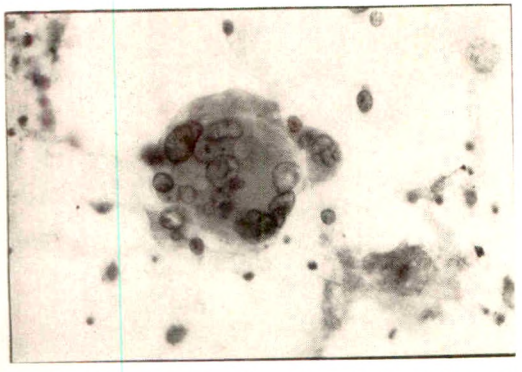


Fig. 1—Tumor giant cell with multiple malignant nuclei in duodenal smear (Papanicolaou, original magnification x400).

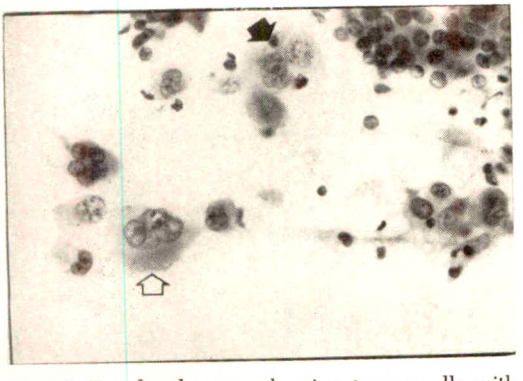


Fig. 2—Duodenal smear showing tumor cells with multiple (light arrow) and single (dark arrow) nuclei (Papanicolaou, original magnification x400).

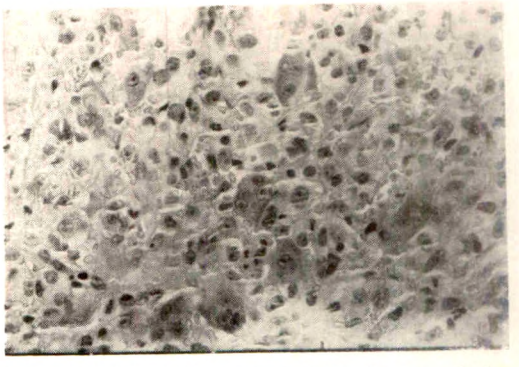


Fig. 3—Histological section of the biopsy of the ulcerating duodenal tumor mass showing a malignant tumor with an epithelial pattern (see well-defined cell borders) and tumor giant cells (Hematoxylin and eosin, original magnification x320).

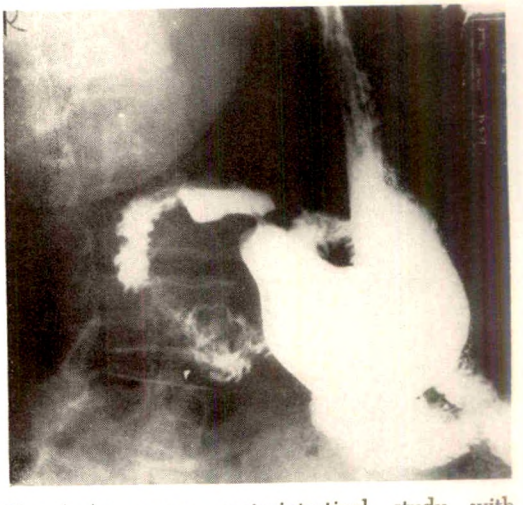


Fig. 4—An upper gastrointestinal study with barium, performed five months after establishing the diagnosis revealing a polypoid mass in the third portion of the duodenum.

was soft, without tenderness. Masses were not palpable. Melena was found on rectal examination. The laboratory tests showed normocytic normochronic anemia of 6.2 gm.% Hgb. WBC was 11,800/cu.mm. Liver function tests were within normal limits. Liver scan revealed a filling defect in the right lobe. Chest x-ray showed residuals of tuberculosis, with a thick right pleura and an emphysematous left lung. Following blood transfusions, endoscopy using the Olympus GIFD-3 endoscope was performed. The esophagus, stomach and duodenal bulb were found to be normal. An actively bleeding polypoid tumor was found in the third part of the duodenum. Several biopsies and a brush for cytology were taken. The smears of the material taken by the brush were stained according to Papanicolaou. They contained numerous malignant cells with large and irregular nuclei and prominent eosinophilic nucleoli. A striking finding was the large number of multinucleated tumor giant cells (Figs. 1 and 2). The same mixture of mononuclear and multinucleated tumor cells was found in the biopsy taken from the polypoid tumor in the duodenum (Fig. 3). The

tumor tissue had an epithelial pattern compatible with that of carcinoma and a diagnosis of giant cell carcinoma of the pancreas was made.[5]

Considering the age and lung disease of the patient it was decided not to operate unless forced to by massive bleeding or any other complication. The tumor was irradiated with 5,000 rads and five months later the patient was doing rather well, without additional episodes of bleeding. A repeat upper gastrointestinal study with barium revealed a polypoid mass in the third portion of the duodenum (Fig. 4).

Comment

Bleeding is a common complication of primary benign or malignant tumors of the duodenum.[6-8] Metastasis to the duodenum can also be the cause of upper gastrointestinal bleeding.[9, 10] Carcinoma of the pancreas can be the cause of occult or massive bleeding from the gastrointestinal tract usually because of direct necrotizing infiltration of the duodenal wall.[3, 4] The tumor can also obstruct the duodenum and thus stimulate acid secretion producing a bleeding peptic ulcer.[11] Hemobilia, caused by pancreatic tumor, was also reported.[12] In most instances the bleeding appears late in the course of the disease and is accompanied by other symptoms. Gastrointestinal bleeding as the presenting symptom of carcinoma of the pancreas has so far been reported in three cases.[4, 13, 14] In two of them, however, it was accompanied by either steatorrhea or epigastric pain. In the case reported here gastrointestinal bleeding was the first and only manifestation of the pancreatic carcinoma. The fact that the barium study of the upper gastrointestinal tract was interpreted as compatible with duodenal ulcer has already been reported in several cases.[14]

Whereas the diagnosis of pancreatic carcinoma is usually established on tissue obtained at operation, in the case reported, a brush for cytology, taken during endoscopy provided the diagnosis. This diagnosis was confirmed also by the endoscopic biopsies. Endoscopic biopsies and cytologic brushes are now commonly used to diagnose malignant tumors in the gastrointestinal tract.[16, 17]

To our knowledge, the diagnosis of giant cell carcinoma of the pancreas, which is a rare variant of carcinoma of the pancreas,[5] has never been made cytologically before. The only comparable case is that published recently by Stransky and LeGolvan,[18] but they used the name intraduodenal sarcoma.

The case presented illustrates once more the efficacy of endoscopy in the diagnosis of upper gastrointestinal bleeding and demonstrates the possibility of establishing cytologically the diagnosis of carcinoma of the pancreas on material obtained by the brush during endoscopy.

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Clinical Vignette

Chronic Idiopathic Pseudo-obstructive Bowel Disease

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An illness characterized by recurrent episodes of small bowel obstruction is described. The patient, a 79-year old gentleman has been followed for 20 years. During this time he has been hospitalized 19 times. Extensive investigation, including three exploratory laparotomies, have failed to show a cause of the bowel dysfunction. The clinical findings have been similar on each admission. Cramping abdominal pain, vomiting, obstipation often followed by diarrhea, tender distended abdomen, high pitched bowel sounds and abdominal x-rays revealed dilatation of small and large intestine and delayed gastric emptying on various admissions. The failure to demonstrate a recognized etiology for the repeated bowel obstruction over a long period of time warrants a clinical diagnosis of chronic idiopathic intestinal pseudo-obstruction (C.I.I.P.). The age of the patient at the onset of symptoms and the duration of the dysfunction prompted a review of the literature. Twenty-seven reported cases allowed a comparison of this case with the clinical features previously described. Symptomatic therapy, consisting of small bowel decompression by intestinal intubation during the acute episode, was followed by the use of elemental diets given slowly and continuously during the convalescing period. The patient continues to be comfortable and able to maintain his body weight between episodes which, however, seem to be increasing in frequency.

Introduction

Chronic idiopathic intestinal pseudo-obstruction is a relatively rare disease. The primary clinical characteristics are intermittent episodes of cramping abdominal pain, obstipation, abdominal tenderness and distention. Diarrhea may appear later in the course of the episode. Abdominal x-rays show dilitation of the bowel, occasionally with gas-fluid levels indistinguishable from mechanical obstruction. Diagnosis is difficult, other causes of bowel obstruction must be carefully considered. Unfamiliarity with the entity will often lead to unnecessary exploratory laparotomy. The prognosis for morbidity is poor particularly in younger patients.

The course of this disease is described in one patient and compared to 27 cases previously reported in the literature.

L. C., a 79-year old man was admitted on 16 February 1977 to the Omaha Veterans Administration Hospital. He had noted the onset of cramping abdominal pain and vomiting 36 hours prior to admission. The abdomen was tender throughout

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This study was supported in part by the Medical Research Service of the Veterans Administration.

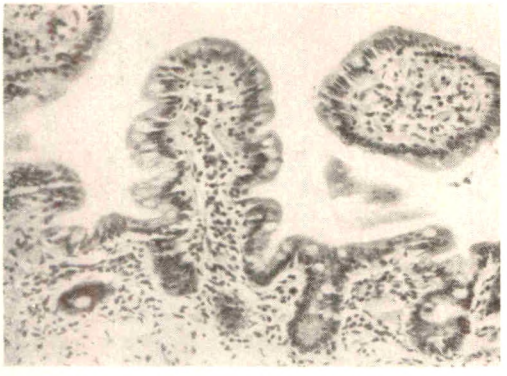


Fig. 1—Essentially normal small bowel mucosa.

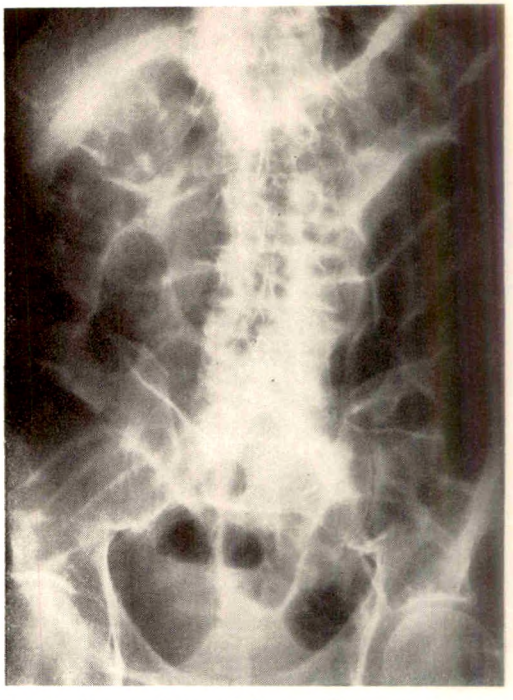


Fig. 2—X-ray of the abdomen demonstrating extensive intestinal dilatation.

and distended. Bowel sounds were hyperactive and high pitched.

Other physical findings were not remarkable for abdominal surgical scars.

Abdominal x-rays demonstrated a dilated small bowel with impaired gastric emptying and colonic dilitation. Following intestinal decompression by Miller-Abbot tube the patient became more comfortable. Diarrhea watery in nature and not malodorous was noted. After several days of intestinal decompression an elemental diet was administered slowly and continuously by nasogastric tube. After several more days the patient was given liquids by mouth and gradually a normal diet was tolerated.

The past history documented 18 previous admissions of the same type. On three occasions exploratory laparotomies failed to demonstrate a recognized etiology for the recurrent bowel obstruction.

Diagnostic studies, often repeated, are listed as follows: a normal rectal biopsy, negative *L.E.* preps, negative urine prophyrin and porphobilinogen, normal 5-HIAA urinary excretion, normal bone marrow, normal lymph node biopsy, normal stool cultures for enteric pathogens and ova and parasites, normal amylase and lipase, normal fat stool content, normal lumbar puncture, normal d-xylose absorption test, normal urinary and serum amino acids, low normal carotene level, normal muscle and prostate biopsy, normal celiac and mesenteric axis arteriograms.

Evaluation of the thyroid showed normal function. Small bowel biopsy was obtained via a Carey capsule as seen in Figure 1 and showed normal small bowel mucosa. There was no evidence of amyloidosis in the rectal biopsy.

A lactose tolerance test was normal, as was a glucose tolerance. The family history contained no evidence of bowel obstruction.

Barium studies of the gastrointestinal tract demonstrated intestinal dilitation (Fig. 2); colonic dilatation (Fig. 3) and delayed gastric emptying (Fig. 4). The patient was receiving no medication when these x-rays were obtained.

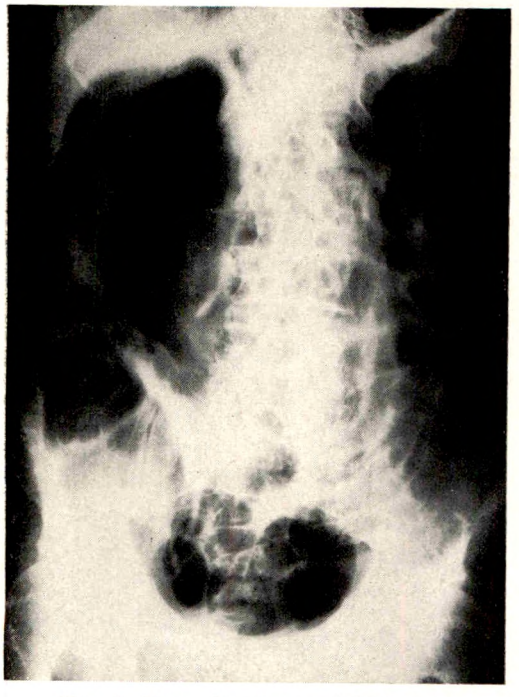


Fig. 3—X-ray showing cecal dilatation.

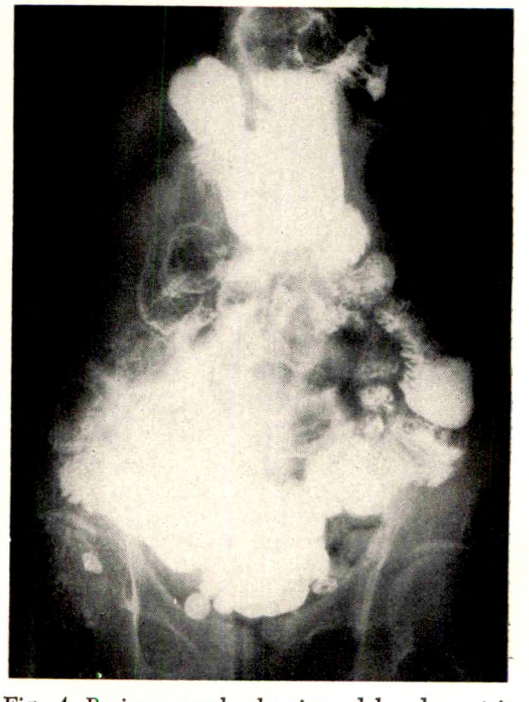


Fig. 4—Barium meal showing delayed gastric emptying.

Comment

Chronic idiopathic intestinal pseudo-obstructive bowel disease is thought to be relatively rare. The clinical diagnosis depends upon exclusion of other entities giving a similar picture, namely scleroderma, dermatomyositis, amyloidosis, myxedema, hypo- and hyperparathyroidism, sprue, mesenteritis, Chagas' disease, *myotonia dystrophica*, Hirschsprung's Disease, drug toxicity and autonomic nervous disorders.[1-3] Scleroderma is particularly difficult to differentiate from C.I.I.P., although the presence of skin lesions and Raynaud's phenomenon in patients with scleroderma aids in establishing this diagnosis.[4]

The entity of C.I.I.P. was clearly recognized by Naish[5] in 1960. Prior to the excellent review of Maldonado[2] in 1970, six other patients were described who warranted this diagnosis.[6-10] Maldonado added five and 14 other cases have been reported excluding the single patient in this report.[3, 11-15]

The pertinent information derived from a review of these patients appears in Table I.

The symptoms and physical findings were remarkably consistent and indistinguishable from those of partial or complete obstruction of the lower small intestine. Colicky pain, vomiting and diarrhea, abdominal distention, hyperactive bowel sounds were seen in most. Symptoms were usually intermittent and recurrent.

Age at onset ranged from 10-64 years without significant difference from the onset to the seventh decade.

Women were apparently more susceptible (16 of the patients) than men (nine of the patients). In three the sex was not reported. The duration of the disease was from six months to 45 years. In 22 of 28

patients the duration was less than 20 years. Four had less than five years' duration and time intervals from 5-10 and 10-20 years included nine patients in each.

Steatorrhea was present in 13 patients and was absent or not reported in the remaining. Usually the fatty stools were associated with bacterial overgrowth.

Weight loss, anemia of moderate degree and hypoalbuminemia were frequent and probably indicated malnutrition secondary to malabsorption. Significant disease other than C.I.I.P. was infrequent.

One patient had agenesis of one kidney and another had atrophy of the left lobe of the liver.[2] A third had polycystic kidneys with uremia.[11]

A familial incidence was noted in only three patients[2, 3] prior to the more sophisticated studies of Schuffler and Pope.[16, 17]

A total of 57 surgical procedures were performed on these 28 patients. Primarily exploratory laparotomies and/or bowel resections were done. Some improvement was noted after bowel resections but in general the effect was minimal. One patient was relieved of symptoms by an extensive small bowel resection.[6]

An abnormality in bowel motility is the prime clinical feature of this disease and was correspondingly found by x-ray or surgery in each instance. Although abnormal gastric motility was noted by Naish[5] and McClelland[7] recognition of generalized disturbances of motility in the entire gastrointestinal tract has occurred only recently. Two of the paients described by Maldonado[2] had disturbed esophageal motility. A decreased pressure in the lower esophageal sphincter was found in two of three patients by Moss.[3] Schuffler and Pope[13] found esophageal dysfunction, disturbances of peristaltic activity and altered lowered esophageal sphincter (LES) activity in five patients with C.I.I.P. This abnormality of esophageal sphincter and intestine was found in each.

Although the pathophysiology of this disorder is not completely understood, recent studies have shown additional areas of the gastrointestinal tract to be involved and the familial aspects of the disease have been emphasized. The pathology remains a subject of controversy.

A detailed study by light and electron microscopy of sections of small bowel from a patient with C.I.I.P. was made by Schuffler, et al.[17] They found marked thinning of the muscular wall of the intestine and its replacement by fibrous tissue. No abnormalities of the myenteric plexus were demonstrated.

Earlier studies by Smith[18] reported thickening of all muscular layers of the intestinal wall. Most striking in this study, however, was the loss of or distortion of neurones and axons of the myenteric plexus. Proliferation of Schwann cells presumably stimulated by axon loss was also marked. These observations were made on the patients described by Naish[5] and McClelland.[7]

Other studies of the small bowel in C.I.I.P. have shown no abnormalities,[11, 12] thickened bowel wall[8] and thinning of small bowel musculature.[2]

Sullivan, et al[15] studied four patients having typical symptoms of intestinal pseudo-obstruction. They demonstrated aperistalsis of the esophagus with incomplete relaxation of the lower esophageal sphincter. An abnormal lack of increased duodenal motor activity when stimulated by distention was demonstrated as well as decreased colonic activity.

Secretin and prostigmine restored normal activity to the duodenum and colon, respectively. The authors concluded that exogenous neurohormonal stimulation re-

TABLE I

CLINICAL CHARACTERISTICS OF CHRONIC IDIOPATHIC INTESTINAL PSEUDO-OBSTRUCTION

Patient	Reference number	Age onset	Duration (yr.)	Sex	Steatorrhea	Motility		Bacterial overgrowth	Surgery
						Esophagus	Small intestine		
1	5	24	12	M	yes	—	+	—	1
2	6	43	16	M	yes	—	+	—	1
3	7	50	5	F	yes	—	+	—	1
4	8	29	19	M	—	—	—	—	1
5	8	16	16	F	—	—	+	—	1
6	9	17	2	F	yes	—	—	yes	2
7	10	31	14	M	yes	—	+	yes	—
8	2	27	14	M	yes	—	+	—	4
9	2	18	34	M	yes	+	+	yes	4
10	2	20	5	F	—m	—	N	—	2
11	2	37	6	M	—	—	+	—	9
12	2	32	18	M	—m	+	+	—	7
13	1	15	7	F	—	—	—	—	7
14	1	14	8	F	—	+	—	—	5

TABLE I (*continued*)

CLINICAL CHARACTERISTICS OF CHRONIC IDIOPATHIC INTESTINAL PSEUDO-OBSTRUCTION

Patient	Reference number	Age onset	Duration (yr.)	Sex	Steatorrhea	Motility		Bacterial overgrowth	Surgery
						Esophagus	Small intestine		
15	1	15	1	F	—	+	—	—	3
16	11	47	12	F	yes	N	+	—	0
17	12	49	4	F	—	N	+	—	0
18	13	20	40	M	yes	+	+	yes	1
19	13	12	45	F	yes	+	+	yes	0
20	13	20	13	F	yes	+	+	yes	0
21	13	50	13	F	yes	+	+	yes	0
22	13	15	0.5	F	yes	+	+	yes	0
23	14	51	2	F	no	—	+	yes	2
24	15	28	4	F	yes	+	+	—	2
25	15	64	9	—	yes	+	+	—	2
26	15	39	29	—	—	+	+	—	2
27	15	53	8	—	no	+	+	—	0

— Not reported; N Normal; + Abnormal

stored normal activity in impaired physiologic neural response. This work confirmed the more generalized involvement of the gut and suggested that in some cases physiologic neural dysfunction was present but response to exogenous neurohumeral stimulation was normal.

In a careful manometric evaluation of 12 relatives of the patient previously described,[17] four were found to have mild dysphagia and abnormal esophageal manometric studies.[16] Abnormal bladder function, indicating a flaccid muscle tone and bilateral ureteral reflux, was also present in two of the relatives. The abnormality was termed hereditary hollow visceral myopathy and proposed the inheritance as a dominant trait of various expressivity.[16, 17]

Our patient is similar to others in presentation except for his older age. The results of barium studies by x-ray show distention of the small bowel and colon. There has been no documentation of malabsorption or bacterial overgrowth. Esophageal function as evaluated by ciné-esophograms is normal. The urinary bladder and ureters do not appear to be affected. During the 20 years that this patient has had C.I.I.P. many drugs or combination of drugs have been utilized with minimal effect. Analgesics have relieved pain and nasogastric suction has relieved distention. Anticholinerics, urecholine and antibiotics aimed at intestinal bacterial overgrowth were ineffective.

An elemental diet, given slowly and continuously after control of acute symptoms of obstruction by nasogastric suction, has been of value.

Conclusion

A case of pseudo-obstruction involving primarily the small bowel is described and delayed gastric emptying and colonic distention were also demonstrable by x-ray studies. The chronicity of the disease, the difficulty in diagnosis, the lack of consistent findings at laparotomy are outlined. A therapeutic program using elemental diets and nasogastric suction is of aid in controlling symptoms. A review of the literature indicates an increasing incidence or recognition of this disease. Basic pathology involves the myenteric plexus and/or the muscular wall of the gastrointestinal system.

A familial incidence is clearly demonstrated in some cases and involvement of the esophagus, colon have been demonstrated in C.I.I.P.

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Clinical Vignette

Massive Gastrointestinal Bleeding from Tuberculosis of the Small Intestine

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Massive bleeding from intestinal tuberculosis is rare. A case of massive bleeding from ulcerations in the proximal ileum is presented. With active pulmonary tuberculosis, intestinal tuberculous ulcerations should be included in the differential diagnosis of gastrointestinal bleeding.

The incidence of gastrointestinal tuberculosis in patients with active pulmonary tuberculosis ranges from 3-90%.[1-4] The wide range reflects the varied severity of the pulmonary infection. The more extensive the pulmonary infection, the greater is the likelihood of gastrointestinal involvement.[3, 4] The pathologic intestinal lesion may be ulcerative, nodular, or a combination of both types.[1, 4-6] Massive bleeding is said to be very rare even in the ulcerative type because of an obliterative endarteritis which is part of the tuberculous process.[4-6, 8-10] This reports a case of massive intestinal bleeding from tuberculous ulceration of the small bowel.

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Case Report

The patient is a 29-year old black carpenter admitted on 17 November 1976, for brisk rectal bleeding.

In February, 1972, the patient first presented to the Atlanta Veterans Administration Hospital with right pleural effusion. The pleural biopsy revealed caseating granuloma, while cultures of both pleural fluid and biopsy grew *Mycobacterium tuberculosum*. The patient subsequently took isoniazide for four months and ethambutol for one year. A chest x-ray in May, 1973, showed complete resolution of the effusion.

In June, 1975, the patient returned complaining of anorexia, weight loss and night sweats. A chest x-ray was interpreted as normal and the patient was lost to follow-up. He subsequently developed diffuse abdominal cramps which persisted up to the time of admission.

Three months prior to admission he noted a small amount of blood in the stool. On admission he had brisk rectal bleeding.

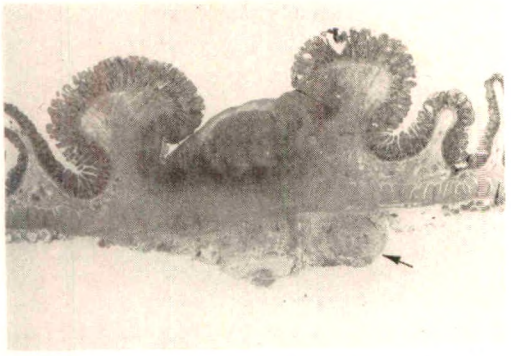


Fig. 1—There is destruction of the mucosal surface with an underlying leucocytic inflammatory reaction. Arrow indicates position of the serosal granulomata (Hematoxylin and eosin, original magnification x4.5).

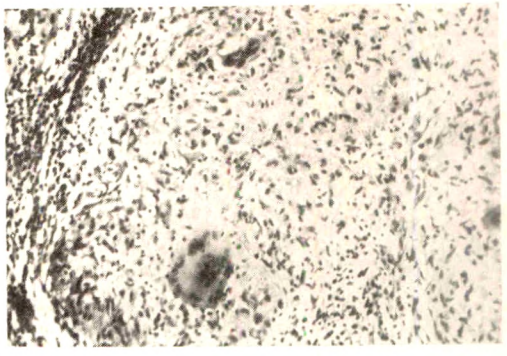


Fig. 2—The serosal granuloma showing necrosis, epithelioid cells, giant cells and lymphocytes (Hematoxylin and eosin, original magnification x200).

There was no history of hematemesis, melena, recent aspirin ingestion or bruisability. A 9 kg. weight loss was detected. The patient was thin but in no distress. Temperature, 36.5° C; blood pressure, 140/110 mm. Hg.; pulse, 104/min. When the patient assumed the erect position, the blood pressure dropped to 110/80 and the pulse rose to 130. The skin was nonicteric and no telangiectasia, ecchymosis or petechia were noted. Examination of the abdomen revealed no masses, organ enlargement, or tenderness. The rectum was normal and proctoscopic examination revealed no hemorrhoids; fresh blood was seen coming from above the 10 cm. level. Nasogastric aspiration was negative for blood.

The chest x-ray showed a reticulonodular infiltrate with cavitation in the left upper lobe. White cell count, 4,000; hematocrit, 31%; platelet count, 101,000; prothrombin time, 10.3 sec. with a control of 12.3; partial thromboplastin time, 22.8 with a control of 32; BUN, 12 mg./dl. and albumin, 3.0 gm./dl. Sputum smears revealed acid fast bacilli.

On the first hospital day, the patient received four units of blood and hematocrit stabilized at 37%.

On the third day, massive rectal bleeding recurred and celiac and superior mesenteric arteriography was performed; no source of bleeding was identified. Since the patient continued to bleed, a laparotomy was performed. After intubation, esophagogastroduodenoscopy was performed and no source of bleeding was found. Blood was noted only in the ileum and colon. Three small areas of hyperemia and edema were present on the mesenteric side in the proximal ileum; each area was resected. Postoperatively there was no further bleeding; a proctosigmoidoscopy, barium enema and small bowel series were normal.

The resected specimens showed circumferential ulcers measuring 1 cm. in width. Numerous polymorphs, monocytes and lymphocytes were noted at the base of the ulcer. The infiltrate extended down to the muscular coat and laterally into the adjacent submucosa (Fig. 1). Increased capillary vascularity occurred within these areas while small arteries disclosed an obliterative endarteritis. Acid fast bacilli were present. Within the serosa, there were small conglomerate tubercles with central necrotic areas surrounded by epithelioid cells with many lymphocytes. Langhan's giant cells were also present (Fig. 2). *Mycobacterium tuberculosum* was recov-

ered by culture from one of the jejunal ulcers as well as from sputum.

Comment

Massive intestinal bleeding is a rare complication of tuberculous enteritis. This patient bled massively, requiring 11 units of blood, from intestinal tuberculous ulcerations.

The setting of active pulmonary tuberculosis, vague abdominal pain, weight loss and small amounts of blood in the stool suggest the diagnosis of intestinal tuberculosis.[4, 6, 8] The patient's young age is not unusual, since tuberculous enteritis is most frequent in the third and fourth decades.[2, 4] The pathologic findings of short diseased segments of the ileum is common, although it is unusual to have proximal ileum involvement without involvement of the terminal ileum.[4-6] The granulomas in the bowel wall may be noncaseating and the ulcers circumferential[4, 7] which can lead to bowel obstruction.[5] The explanation for the rarity of massive bleeding is the pathologic finding of an obliterative endarteritis within the ulcer. In the presence of active pulmonary tuberculosis, tuberculous ulceration of the intestine should be considered in the differential diagnosis of massive intestinal bleeding.

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Clinical Vignette

Delayed ("Blow-out") Perforation of Sigmoid Following Diagnostic Colonoscopy

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A case has been described in which perforation of the sigmoid colon occurred three days following simple diagnostic colonoscopic examination. The desirability is indicated for including the possibility of this occurrence in the informed consent. Administration of stool softener and use of low-residue diet for several days following diagnostic and therapeutic colonoscopy may be of value in averting the occurrence of this catastrophe.

Colonic perforation is a well-recognized hazard of diagnostic fiberoptic colonoscopy. Its incidence has been documented to range from 0.1-0.9%.[1-4]

This dreaded event usually is recognized immediately when it occurs during a procedure; less frequently, it becomes manifest at some time during the 24-hour period following instrumentation. Later occurrence of perforation is uncommon. In a series of 5,244 diagnostic colonoscopic examinations, one instance of perforation developed after 24 hours (0.02%).[1] In another series of 200 examinations, one instance of perforation of the sigmoid colon occurred five days after colonoscopy.[5] We are reporting a case in which perforation of the sigmoid colon occurred three days following a simple diagnostic colonoscopic examination.

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Report of Case

A 57-year old caucasian male was admitted to the Long Beach Veterans Administration Hospital complaining of sudden onset of cramping abdominal pain and hematochezia which occurred immediately following a normal bowel movement. There was no previous history of gastrointestinal bleeding. He was being treated for *discoid lupus* and seropositive rheumatoid arthritis with Ascriptin®, Indocin®, and Penicillamine® in therapeutic doses. Physical examination demonstrated joint deformities, consistent with his rheumatoid arthritis and the presence of burgundy-colored material in the rectum. Upper gastrointestinal panendoscopy revealed no abnormality. Sigmoidoscopic examination demonstrated a normal mucosa which the intraluminal blood originating from a source beyond the reach of the instrument.

The hematocrit level remained above 39%, bleeding ceased spontaneously shortly following hospitalization and blood trans-



Fig. 1—Diverticular disease of the sigmoid colon.

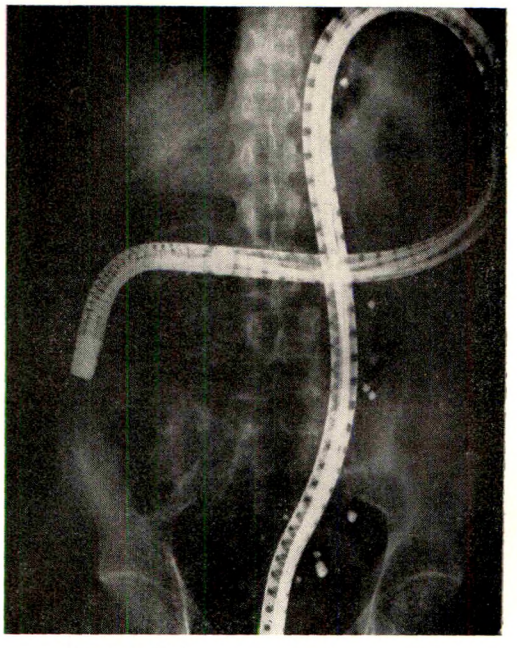


Fig. 2—Colonoscope to the cecum.

fusion was not required. Barium enema examination demonstrated diverticulosis, involving the sigmoid (Fig. 1) and transverse colon and a radiolucent, circular filling defect, in the mid descending colon, which measured 1.5 cm. in diameter, and was interpreted to represent a sessile polyp. Colonoscopy was attempted on the sixth hospital day but the patient did not tolerate the procedure and requested that it be terminated. He was discharged from the hospital and experienced no further occurrence of bleeding during the ensuing month. Colonoscopy, to the cecum, was then accomplished simply, expeditiously and uneventfully and was documented radiographically (Fig. 2). Multiple colonic diverticuli were visualized but, despite careful inspection, polyps were not encountered. During the ensuing 52 hours, he was discharged from the hospital and resumed his customary dietary habits and occupation. Subsequently, he experienced a sensation of soreness and of intermittent griping in both of his lower abdominal quadrants, which radiated proximally, along the course of his colon, to the upper abdominal quadrants. There was no associated fever, nausea, or vomiting. He ascribed these symptoms to the fact that he had not had a bowel movement since his colonoscopy and continued his customary activities, eating lunch and dinner, and retired that night as usual. At 3:30 the following morning (68 hours after colonoscopy) he was awakened by abdominal pain which radiated to his right groin, associated with the urge to move his bowels. He went to the bathroom and evacuated a small amount of feces. Immediately thereafter he experienced severe pain in the suprapubic area and cessation of further bowel evacuation. He returned to bed and noted a gradual spread of the pain to the upper abdomen and progressive abdominal distention. He took 3 grains of Codeine for relief. The pain, however, did not subside and he returned to the hospital 14 hours later (82 hours after colonoscopy).

Physical findings at that time showed temperature, 37.5° C; pulse, 102; respiration, 24; blood pressure, 118/66. The ab-

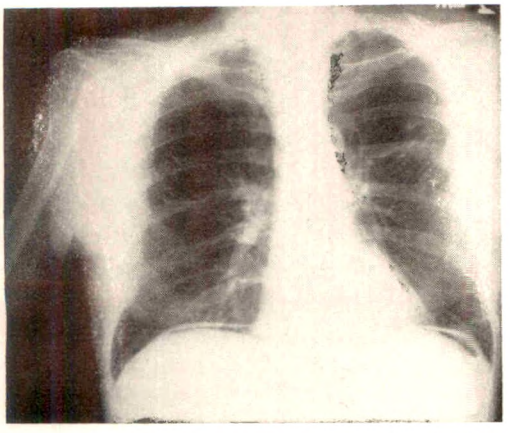


Fig. 3—Free air, intraperitoneally, indicating perforation of the hollow viscus.

dominal girth was slightly increased, the bowel sounds were absent and the lower abdominal quadrants were diffusely tender but rebound tenderness was not elicited.

The significant laboratory findings included: hematocrit, 39%; hemoglobin, 13 gm.; WBC, 3,500 with 40% polymorphonuclear leucocytes, 55% band forms and 5% lymphocytes; BUN, 24 mg.% and normal amylase and lipase values. Acute abdominal radiographic series demonstrated the presence of free air in the peritoneal cavity (Fig. 3).

Surgical operation was performed 84 hours after colonoscopy and 16 hours following onset of acute abdominal symptomatology, disclosing the presence of copious amounts of free pus in the peritoneal cavity. The sigmoid colon was adherent to the pelvic brim, effectively sealing off the true pelvis. It was freed by finger-dissection exposing an abscess cavity containing fecal material and a circular defect in the wall of the sigmoid colon, measuring 2 cm. in diameter, from which the intestinal contents had escaped. The hole was located on the anterior wall, in an area containing diverticuli, approximately 15 cm. from the peritoneal reflection, and mid way between the mesenteric and antimesenteric borders. Its periphery was slightly ragged but not indurated. Lacerations were not visualized in the mesentery of the sigmoid.

The perforation was oversewn and a transverse colostomy was performed for purpose of decompression. His postoperative course was uneventful and the colostomy was closed ten weeks later.

Comment

The sigmoid is the segment of colon which is most prone to injury during diagnostic colonoscopy. The factors responsible for this phenomenon include disease conditions which have a penchant for affecting this area (diverticular disease, pericolic pelvic adhesions, strictures, carcinoma), manipulations which overstretch this loop of large intestine ("persuasive pressure", "slide-by", "alpha-maneuver", use of external or internal mechanical straighteners of the sigmoid), and over distention with air, occasioned through negligence or by a faulty air-delivery system.[6]

Trauma, inflicted by a fiberoptic instrument, to the wall of the sigmoid colon, may produce a perforation whose clinical appearance, as mentioned, may be immediate or may be delayed. The latter is probably created by manipulations which cause overstretching of the sigmoid loop. This produces laceration of the serosa and muscular coat, permitting the mucosa to herniate and, eventually, to rupture.[7-9] Iatrogenically created lesions of this sort measure 1.5-2.0 cm. in length and occur on the antimesenteric border.

In the case which we are reporting, the perforation occurred in an area of diverticulosis, making it impossible to exclude entirely the possibility that it may have resulted from diverticular rupture unreleated to the instrumentation.

The mild abdominal symptoms (soreness and intermittent griping sensation) which appeared 52 hours following colonoscopy and 16 hours prior to acute perforations, were attributed, by the patient, to the fact that his bowels had not moved since the examination. While, in retrospect, these symptoms may have been predicated upon localized pathology and portended the catastrophe which eventuated, it is possible that the interpretation which the patient placed upon them may very well have been correct. The large diameter (2 cm.) of the defect in the wall of the sigmoid colon, the absence of inflammation and induration of its margin, and the fact that it was easily closed with sutures,[10] fortify the speculation that the delayed perforation derived from the above-described pathogenesis, rather than from an unrelated, fortuitous rupture of a diverticulum. On the other hand, the location of the perforation mid way between the mesenteric and antimesenteric border on the anterior wall would favor a diverticular etiology.

The precipitous occurrence of perforation in our patient, in association with the act of defecation, is significant and interesting. The elevation of intraluminal pressure which is created during the process probably causes "blow-out" of the weakened area in the bowel wall. This phenomenon may be more prevalent than is generally appreciated; it is observed especially in those delayed perforations which occur at the site of colonoscopic electrosurgical polypectomy. (Recently, a colleague related his experience with two patients who developed delayed perforation at the time of the first bowel movement following electrosurgical polypectomy in the sigmoid colon.) Thus, it would appear propitious to include in the informed consent for diagnostic, as well as for therapeutic, colonoscopy, the possibility that delayed ("blow-out") perforation may occur. The patient should be cautioned to inform his physician if abdominal symptoms should develop during the several days after colonoscopy.

Finally, use of a low-residue diet and administration of a stool softener, for several days following these procedures, may reduce the fecal mass as well as the degree of straining required for its evacuation. In consequence, these important factors in the pathogenesis of "blow-out" perforation of a weakened area may be minimized.

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The Radiology Corner*

The Value of Postevacuation Radiographs of the Bowel To Distinguish Free Perforation From a Confined Extraluminal Barium Collection

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If free extravasation occurs during barium enema examination of the bowel, postevacuation radiographs will show spreading of the barium. Conversely, if a walled-off extraluminal cavity is filled by the barium, the postevacuation radiographs will demonstrate no change or a decrease in size of the area of extraluminal barium. Use of this sign improved diagnostic accuracy 28% (from 60-88%).

Complications of barium enema examination consist of intraperitoneal and extraperitoneal perforation of the colon, barium granulomas of the rectum, water intoxication, retroperitoneal emphysema and intravasation of barium (which is usually fatal).[1-9] When extraluminal barium is recognized, the radiologist must determine if it is 1. free extra- or intraperitoneal barium and feces that have spread from an acute rent in the bowel wall or 2. a collection of barium within a walled-off cavity that communicates with the bowel. The distinction between free and walled-off barium is of grave clinical significance because perforated bowel requires immediate surgical intervention, while a walled-off cavity does not.

We have found a useful sign for making this determination. In patients with perforated bowel, postevacuation radiographs will show spreading of the extraluminal barium. In patients with a walled-off extraluminal cavity, postevacuation radiographs will show no change or a decrease in the extraluminal area that is opacified. Extraluminal barium may not appear until the time of the postevacuation radiograph; in such cases a second postevaculation radiograph is needed to ascertain if free extravasation of barium has occurred.

We investigated the accuracy of this differential sign.

Material and Methods

Seven consecutive cases that demonstrated extraluminal barium (Table I) were gathered to be viewed by seven third-year residents in diagnostic radiology. Three of the cases demonstrated free intra- or extraperitoneal extravasation of barium; the other four were examples of extraluminal barium in a walled-off cavity that communicated with the bowel. Only cases with postevacuation radiographs available and surgical proof of the interpretation of the cause of the extraluminal barium were used in the study. The diagnostic sign was explained to the seven residents and they were then asked to independently analyze the pre-evacuation (showing the bowel filled with barium) and the postevacuation

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TABLE I

CASE MATERIAL

Case	Age, sex	Clinical history	Site of perforation	Possible cause	Extraluminal barium free? (radiographic diagnosis*)
1	70, M	Chronic ulcerative colitis	Rectum	Inflation of balloon catheter	Yes—perirectal and extraperitoneal barium
2	60, M	Descending colostomy	Descending colostomy stoma	Inflation balloon catheter inside stoma	Yes—intraperitoneal barium
3	44, M	Heroin addict, endocarditis, blunt abdominal trauma, sigmoidoscopy 24 hr. before barium enema	Sigmoid	Rupture of diseased area of colon by increased intraluminal pressure	Yes—intraperitoneal barium
4	70, F	Transsacral peritoneal resection (12 mo. before) for low sigmoid adenocarcinoma	Anastomosis at rectosigmoid colon	Postoperative anastomotic leak	No—walled-off retrorectal cavity
5	66, F	Diverticulitis	Sigmoid	Ruptured diverticulum	No—large left retroperitoneal abscess cavity
6	50, F	Diverticulitis, multiple operations	Cecum	Ruptured diverticulum or anastomotic leak	No—pelvic abscess with sinus tracts to vagina, rectum, perineum
7	77, M	Diverticulitis, bilateral aortoiliac graft	Sigmoid	Ruptured diverticulum	No—abscess surrounding righ limb of graft

* Surgically confirmed.

radiographs of each case. They were to decide whether the bowel perforation was free or not.

A control group of seven board certified diagnostic radiologists, most of whom were one year senior to the residents, also independently analyzed the cases, but without knowledge of the proposed diagnostic sign.

RESULTS

Over all accuracy was 28% higher (88% contrasted to 60%) for the group that used the diagnostic sign (Table II).

TABLE II

RESULTS

Confirmed diagnosis	Case	Residents using proposed sign							Radiologists without use of sign						
		A	B	C	D	E	F	G	H	I	J	K	L	M	N
Perforation	1	+	+	+	+	+	+	+	−	−	−	−	−	−	+
	2	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	3	+	+	+	−	+	+	−	+	+	+	+	+	−	+
Walled-off cavity	4	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	5	+	+	+	+	−	+	−	−	+	−	−	+	+	−
	6	+	+	+	+	+	+	+	−	+	−	+	−	−	−
	7	+	+	+	+	−	+	−	+	+	−	+	−	−	+
	Over all accuracy	88% $\frac{43}{49}$							60% $\frac{30}{49}$						

+ = correct diagnosis, − = incorrect diagnosis.



Fig. 1a



Fig. 1b

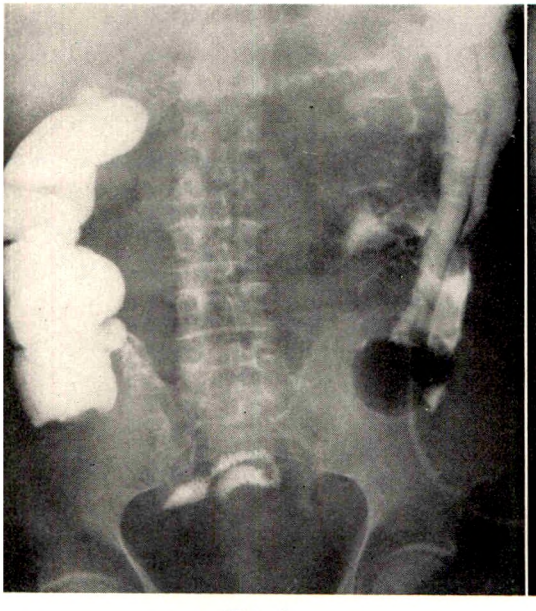


Fig. 2a



Fig. 2b

Fig. 1—Case 1. *a.* Pre-evacuation and *b.* postevacuation radiographs. Small area of barium extravasation in the rectal wall increases into perirectal and extraperitoneal tissues on the postevacuation radiograph. The perforation was associated with inflation of the rectal balloon catheter.

Fig. 2—Case 2. *a.* Pre-evacuation and *b.* postevacuation radiographs. Spreading of intraperitoneal barium is seen in a patient with a perforation associated with a balloon catheter inflated inside a colostomy.

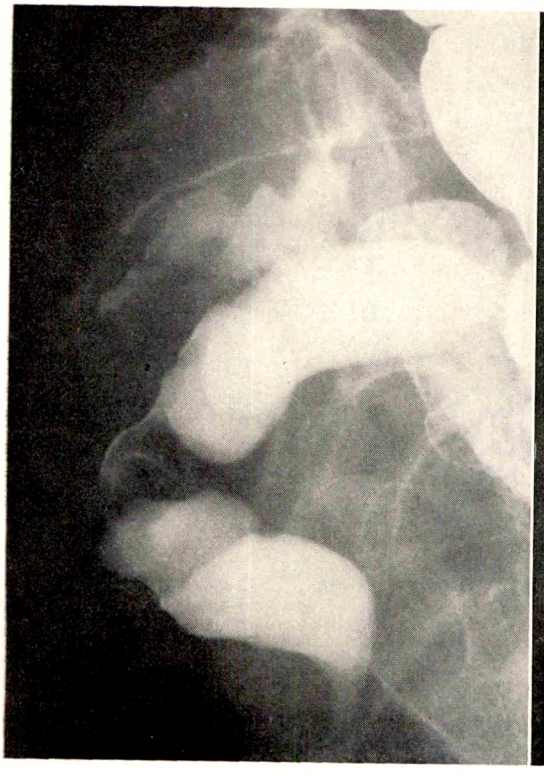


Fig. 3a

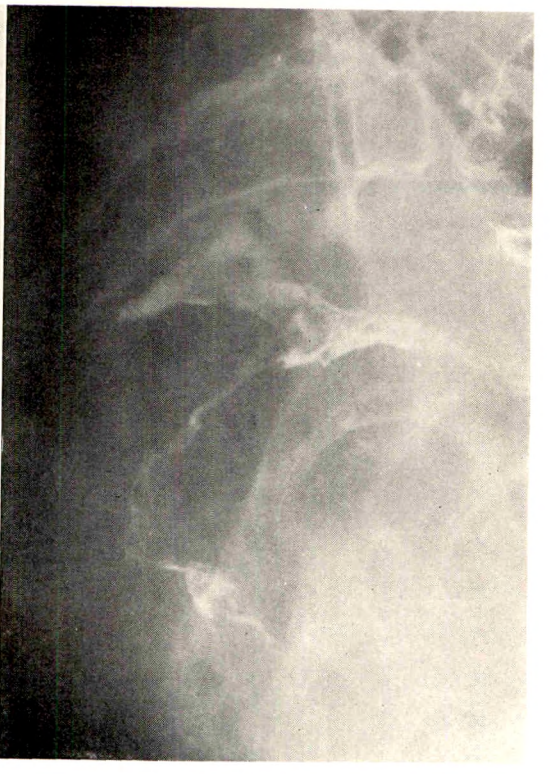


Fig. 3b



Fig. 4a



Fig. 4b

Fig. 3—Case 4. *a.* Pre-evacuation and *b.* postevacuation radiographs. The size of the extraluminal barium decreases. The patient has an old, retrorectal, walled-off, anastomotic leak.

Fig. 4—Case 7. *a.* Pre-evacuation and *b.* postevacuation radiographs. The amount of extraluminal barium remains unchanged in a patient with a walled-off cavity surrounding the right limb of an aortoiliac graft. At surgery this cavity was found to communicate with a sigmoid diverticulum.

Although the control group of radiologists were more experienced, without the proposed sign their accuracy was clearly lower than that of the residents.

The results of evaluation of Case I (Figs. 1a and 1b) indicate that the sign was useful in identifying a small free perforation. On the other hand, results for Cases 2 (Figs. 2a and 2b) and 3 indicate that the knowledge of the sign produced no change in accuracy in diagnosing large free perforation.

The data for Cases 4, 5, 6 and 7 (Figs. 3a and 3b and 4a and 4b) indicate that without the proposed sign, more false positive diagnoses of free perforation were made, when only a walled-off extraluminal cavity was present.

Comment

Several radiographic findings distinguish free perforation from a walled-off cavity. A sinus tract or cavity communicating with the bowel is present if the barium collection has a discrete contour. The perforation is extraperitoneal if the barium streaks irregularly and outlines retroperitoneal structures. The perforation is intraperitoneal if barium outlines the outside of bowel walls, the falciform ligament, or the undersurface of the hemidiaphragms, or if it lies in the paracolic gutters.

In addition to the shape of the barium collection, the cases reported here illustrate that comparison of the size of the extraluminal space on preevacuation and postevacuation radiographs is another useful differential point. If free extravasation occurs during barium sulfate enema, subsequent postevacuation radiographs will show increased spread of the contrast material. Noveroske[4] studied the intracolonic pressures that develop during the administration of a barium enema and the colon's tolerance of that pressure. The stripping and squeezing action that occurs with contraction of the smooth muscle of the colon and the high intraluminal pressures that occur during evacuation produce the extravasation of barium that is seen after evacuation.

This sign does not apply to extravasation during an enema examination performed with iodinated water-soluble contrast medium. Because water-soluble agents may be absorbed by the peritoneum by the time the postevacuation radiograph is obtained, the area of extraluminal opacification may appear smaller. As a result of the peritoneal absorption the renal calyces, ureters, and bladder sometimes opacify.[10]

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The Last Page

QUESTIONS IN GASTROENTEROLOGY

MICHAEL RUOFF, M.D., F.A.C.G.*
New York, N. Y.

The Last Page appears as a regular feature in each issue of THE AMERICAN JOURNAL OF GASTROENTEROLOGY.

The questions that follow have been prepared exclusively from material in the current issue of the Journal and the page on which the answer can be found is indicated with each question.

One way for regular readers of the journal to utilize this feature is to scan *The Last Page* and attempt to answer the questions before reading the Journal. Then, when the articles have been read, return to *The Last Page*, again try to answer the questions and finally refer to the page locations that are provided in order to confirm your answers.

For each question, one or more responses may be correct, or none may be correct.

1. BACTERIAL OVERGROWTH OF THE PROXIMAL SMALL BOWEL:

   A. Can cause ultrastructural changes in the epithelium without apparent invasion into the epithelial cells.

   B. Is accompanied by bile salt deconjugation.

   C. Can result from mecamylamine-induced intestinal stasis.

   D. Will have varying effects on the intestine depending on both quantitative and qualitative differences in the bacterial composition.

(Page 254)

2. STUDIES OF THE LIVER UPTAKE OF CONJUGATED BILIRUBIN IN THE RAT HAVE REVEALED THAT:

   A. The conjugated bilirubin enters the liver cells by simple diffusion.

   B. Net hepatic clearance of unconjugated bilirubin is three-fold greater than that of conjugated bilirubin.

   C. Uptake is inhibited by unconjugated bilirubin.

   D. Uptake is stimulated by sulfobromophthalein.

(Pages 262, 263)

3. INTRAVENOUS SECRETIN HAS THE FOLLOWING EFFECTS ON THE RAT COLON:

   A. Stimulates acetic acid and sodium acetate-evoked colonic mucus secretion.

   B. Increases the net sodium absorption.

   C. Interferes with the colonic absorption of sodium acetate.

   D. Reduces the resistance to the transport of lipid soluble unionized acetic acid.

(Page 268)

4. CORRECT NEEDLE PLACEMENT DURING THIN NEEDLE PERCUTANEOUS TRANSHEPATIC CHOLANGIOGRAPHY IS DETERMINED BY NOTING THAT:

   A. When a vein or artery is entered rapid centripetal clearing of dye occurs.

   B. When a biliary duct is entered slow filling occurs.

* Assistant Professor of Clinical Medicine, New York University School of Medicine.

C. Puddling of contrast occurs when the parenchyma is injected.

D. Fine linear collections of contrast move towards the vertebra when the lymphatics are punctured.

(Page 270)

5. GLUCAGON:

A. Depletes the zymogen granules of pancreatic acinar cells.

B. Depresses pancreatic exocrine secretion.

C. Has identical biological properties whether secreted from the pancreas or from the jejunum.

D. When compared to placebo produces no significant difference in the outcome of acute pancreatitis.

(Page 279)

6. STUDIES OF PAROTID SECRETION AFTER SECRETIN STIMULATION REVEAL THAT:

A. Pancreatic pathology appears to be associated with decreased salivary flow after secretin.

B. Basal salivary flow is depressed in pancreatitis.

C. Criteria can be established whereby pancreatic disease can be reliably diagnosed on the basis of this secretory response.

D. In alcoholic pancreatic insufficiency protein output in saliva is increased.

(Page 284)

7. TREATMENT OF THE ZOLLINGER-ELLISON SYNDROME WITH H_2 RECEPTOR ANTAGONISTS:

A. Leads to prolonged inhibition of gastric acid secretion after withdrawal of cimetidine.

B. Has been successful for periods up to two and a half years.

C. Inhibits the ability of secretin to increase serum gastrin levels.

D. Significantly increases the fasting serum gastrin level.

(Page 289)

8. PRIMARY AORTODUODENAL FISTULA:

A. Is considerably less common than fistula secondary to reconstructive aortic surgery.

B. Occurs where the third portion of the duodenum rests on the aorta just distal to the origin of the renal arteries.

C. Usually progresses from initial bleed to fulminant hemorrhage within four to six hours.

D. Can only be treated successfully by surgical intervention.

(Page 295)

9. COMPUTED TOMOGRAPHY SCANNING:

A. Will become more useful as scan time decreases.

B. Can be used to direct drainage of abdominal abscesses.

C. Can guide antegrade pyelography and percutaneous nephrostomy.

D. Can be used to direct drainage of hepatic abscesses.

(Page 300)

10. CARCINOMA OF THE PANCREAS:

A. Has undergone a significant change in course and prognosis in the last 30 years.

B. Is usually symptomatic for 15 to 18 months prior to admission to hospital.

C. Is associated with gastrointestinal bleeding early in its course.

D. Requires a high degree of suspicion for early diagnosis.

(Page 304)

11. CHRONIC IDIOPATHIC PSEUDO-OBSTRUCTIVE BOWEL DISEASE:

A. Is clinically diagnosed by excluding other entities giving a similar picture.

B. Presents consistent anatomic and histologic findings at laparotomy.

C. Can present in patients from 10-64 years of age.

D. Can be associated with steatorrhea due to bacterial overgrowth.

(Page 312)

12. TUBERCULOUS ENTERITIS:

A. Is most frequent in the fifth and sixth decades.

B. Involves the proximal ileum, sparing the terminal ileum.

C. Can cause circumferential ulcers that lead to bowel obstruction.

D. Rarely bleeds massively because of an obliterative endarteritis.

(Page 315)

13. SIGMOID PEFORATION FOLLOWING COLONOSCOPY:

A. Has an incidence of 0.1-0.9%.

B. Can occur up to five days after colonoscopy.

C. Usually measures 1.5-2.0 cm. in length and occurs on the antimesenteric border.

D. Is usually due to rupture of a diverticulum.

(Page 320)

14. RADIOGRAPHIC FINDINGS DISTINGUISHING FREE PERFORATION FROM A WALLED-OFF CAVITY INCLUDE:

A. Barium streaking irregularly and outlining the retroperitoneal structures in free perforation.

B. A discrete contour when a communicating cavity is demonstrated.

C. Postevacuation films showing increased spread of contrast material in free extravasation.

D. No change or a decrease in size of the cavity on postevacuation films if a walled-off cavity is filled.

(Page 328)

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SELECTED ABSTRACTS FOR GASTROENTEROLOGISTS

A prospective randomized study of endoscopy and radiology in acute upper gastrointestinal tract bleeding. Dronfield MW, McIlmurray MG, Ferguson R, et al: Lancet 2:1167-1170, 1977.

Preliminary results from a prospective randomized study comparing endoscopic and radiographic accuracy in acute upper gastrointestinal hemorrhage is restoring much confidence in the value of conventional double-contrast radiography.

In 322 equally randomized patients, no difference was found in the management and survival in the two groups, even though the diagnostic yield was higher in the endoscopy group. The number of patients undergoing surgery, the morbidity and mortality rates and the number of excusable diagnostic errors were comparable in the two groups.

This report reinforces the view that competent radiology needs no augmentation by early endoscopy in the management of patients with acute upper gastrointestinal bleeding.

DEMETRIUS PERTSEMLIDIS, M.D., F.A.C.G.

Stimulation of gastric inhibitory polypeptide in normal and duodenal ulcer patients. Cataland S, O'Dorisio TM, Brooks R, et al: Gastroenterology 73:19-22, 1977.

Gastric inhibitory polypeptide (GIP) is one of several intestinal polypeptide hormones, previously defined collectively as enterogastrones. GIP is released from the proximal jejunum in response to a meal containing fat, glucose, or both and can now be measured in the plasma.

In their studies, Cataland, et al were unable to find a correlation between defective release of GIP and peptic ulcer disease. In contrast, they found increased GIP release in response to a mixed meal, compared to controls without duodenal ulcer.

Thus, the search for a more precise definition of the gastric acid hypersecretion in duodenal ulcer continues.

DEMETRIUS PERTSEMLIDIS, M.D., F.A.C.G.

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BOOK REVIEWS FOR GASTROENTEROLOGISTS

Computerized Axial Tomography: edited by G. H. du Boulay, M.D. and I. F. Moseley, M.D. 430 pages, illustrated. Springer-Verlag New York, Inc., New York, N. Y., 1977. Price $34.40.

This time it is the proceedings of the first European seminar on CAT. It's of historical interest only and cannot be recommended to the general reader or specialist at this time.

DAVID A. DREILING, M.D., F.A.C.G.

Gastrointestinal Physiology: edited by Leonard R. Johnson, Ph.D. 164 pages, illustrated. The C. V. Mosby Company, St. Louis, Mo., 1977. Price $7.95.

I like this paperback. It represents an integrated and current course in gastrointestinal physiology given to medical and graduate students. In 150 unpretentious pages the whole story of hormones, motility, secretion, digestion, absorption and gastrointestinal circulation are presented in clear, splendidly illustrated and concise terms. Ideal for licensure and board cramming and only $7.95.

DAVID A. DREILING, M.D., F.A.C.G.

Atlas of Endoscopic Retrograde Cholangiopancreatography: edited by Edward T. Stewart, M.D., Jack A. Wennes, M.D. and Joseph E. Geenen, M.D. 366 pages, illustrated. The C. V. Mosby Company, St. Louis, Mo., 1977. Price $45.00.

We are not wanting for atlases of ERCP. This is a good one, multiauthored, combining roentgenologist and gastroenterologist. There are good sections on technic and complications. The illustrations were carefully chosen to be instructive and they are. The supporting text is brief, clear and educational.

DAVID A. DREILING, M.D., F.A.C.G.

Cholesterol Metabolism and Lipolytic Enzymes: edited by J. Polonovski. 211 pages, illustrated. Masson Publishing USA, Inc. New York, N. Y., 1977. Price $26.00.

This volume is a compilation of papers presented at the 19th International Congress on the Biochemistry of Lipids in September, 1976. The many contributors include prominent investigators in the field of lipid metabolism from the United States, Europe and Israel. The first section of this volume includes papers on recent progress on cholesterol metabolism and the second relates to lipolytic enzymes.

A wealth of information reflecting recent progress in cholesterol metabolism and lipolytic enzymes can be found in this volume.

It is highly recommended to biochemists, gastroenterologists and those interested in lipid metabolism.

DEMETRIUS PERTSEMLIDIS, M.D., F.A.C.G.

1977 Year Book of Medicine: edited by D. E. Rogers, M.D., R. M. Des Prez, M.D., M. J. Cline, M.D., E. Braunwald, M.D., N. J. Greenberger, M.D., P. K. Bondy, M.D. and F. H. Epstein, M.D. 595 pages, illustrated. Year Book Medical Publishers, Chicago, Ill., 1977. Price $23.50.

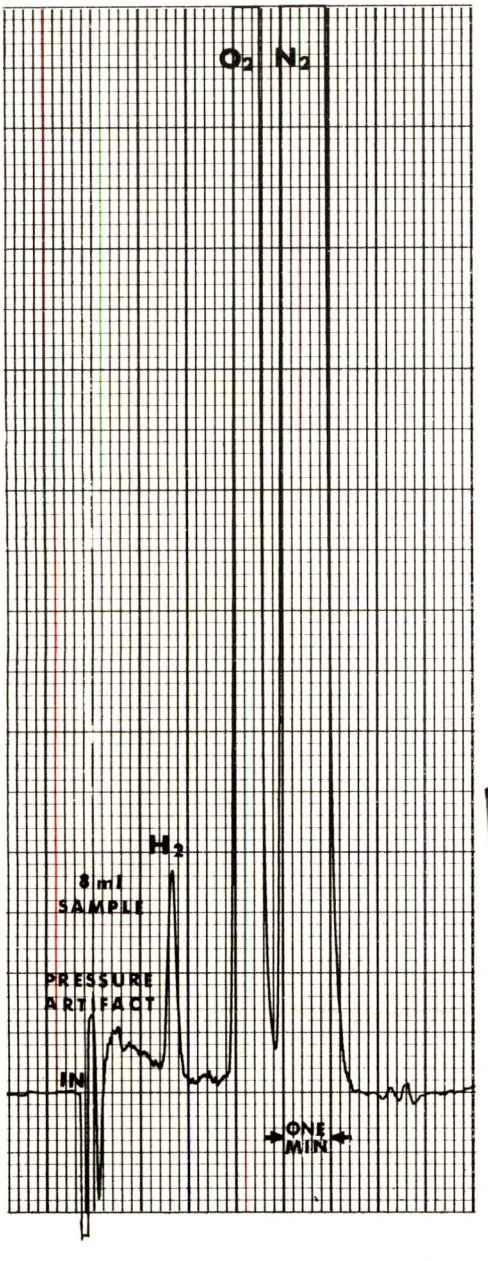
There are seven editors in the seven different sections of this 1977 Yearbook of Medicine. They include David E. Rogers, Professor of Medicine at Cornell University Medical College reviewing infections; Roger M. Des Prez, Professor of Medicine at Vanderbilt summarizing chest diseases; Martin J. Cline, Professor of Medical Oncology at UCLA discussing the blood and blood-forming organs; Eugene Braunwald, Associate Professor of Medicine and Head of Harvard School, Department of Medicine at Peter Bent Brigham, on head and blood vessels; Norton J. Greenberger, Professor and Chairman of the Department of Internal Medicine, University of Kansas Medical Center who considers the digestive system; Philip K. Bondy, Professor of Medicine at The Institute of Cancer Research, Royal Marsden Hospital, London on metabolism and Franklin H. Epstein, Professor of Medicine at Harvard Medical School who reviews kidneys, water and electrolytes.

The strong point of this book is the excellent caliber of the editors for each section. Each editor has selected the articles of major interest over the past year and not only reviewed the articles clearly and succinctly but discussed the papers in an excellent and comprehensive fashion. The review of the literature is frequently so complete that one can read a summary of the article and get a total perspective on the subject by considering the editorial comments which follow. I recommend this book highly to all those interested in medicine, surgery, or other subspecialty areas of medicine which are covered in this book. No physician interested in the fascinating aspects of medicine both from a clinical and research point of view should be without this book on their shelves.

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* Solomons, N.W., Viteri, F.E. and Hamilton, L.H.: Application of a simple gas chromatographic technique for measuring breath Hydrogen. J Lab Clin Med 90:856, 1977.

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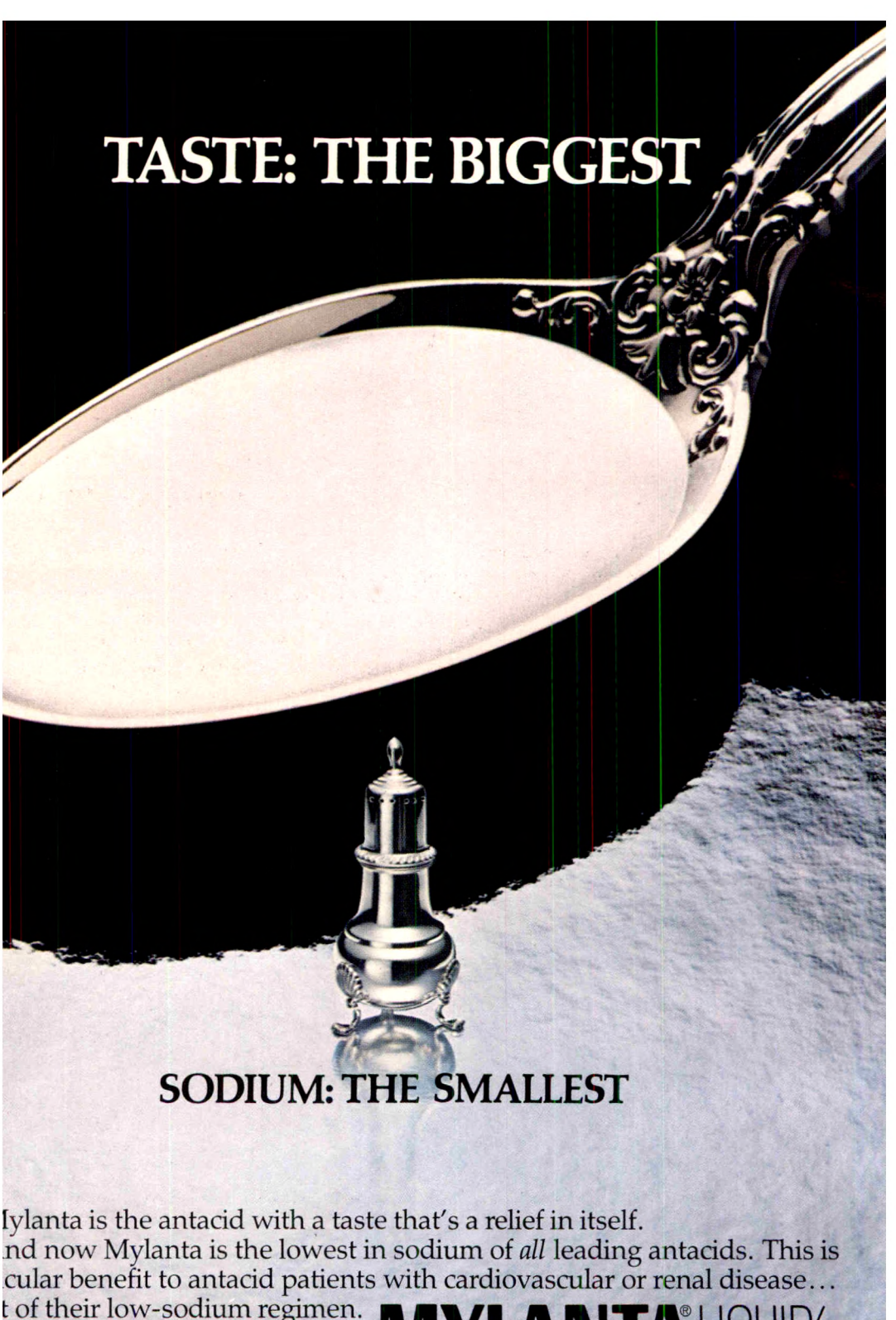
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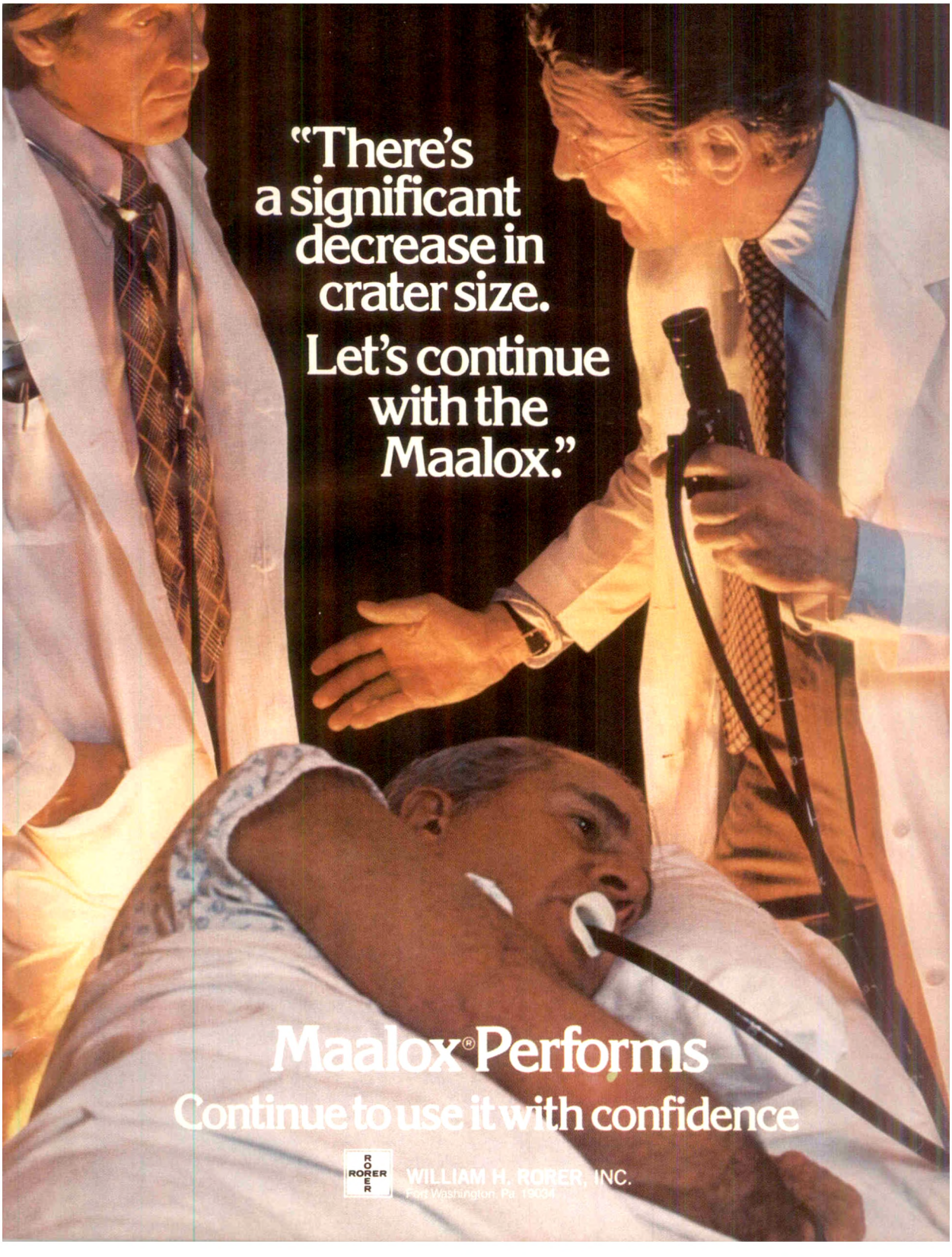
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4. Ansel HJ: Normal Pancreatic Duct. *In:* Atlas of Endoscopic Retrograde Cholangiopancreatography. Edited by Stewart, ET, Vennes JA, Geenen JE. St. Louis, The C. V. Mosby Company, 1977, pp. 43-47.

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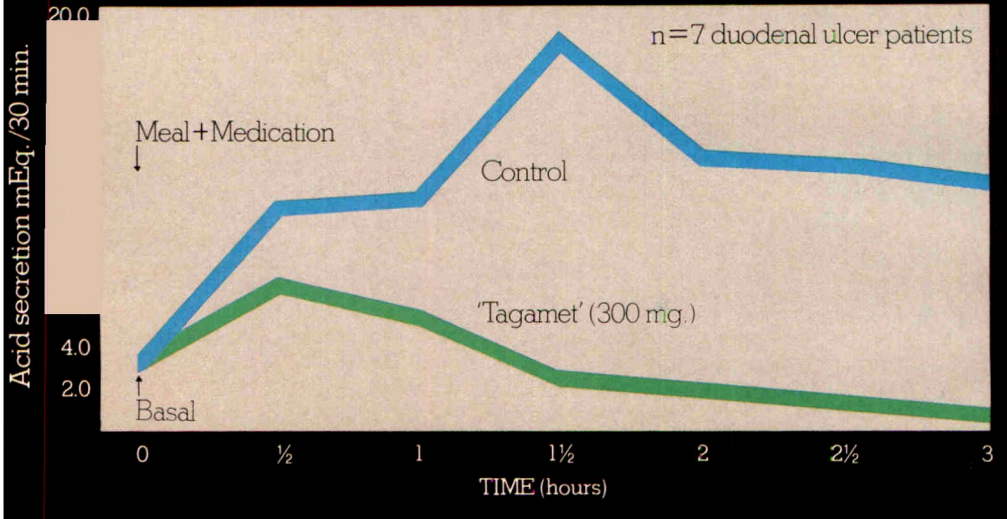
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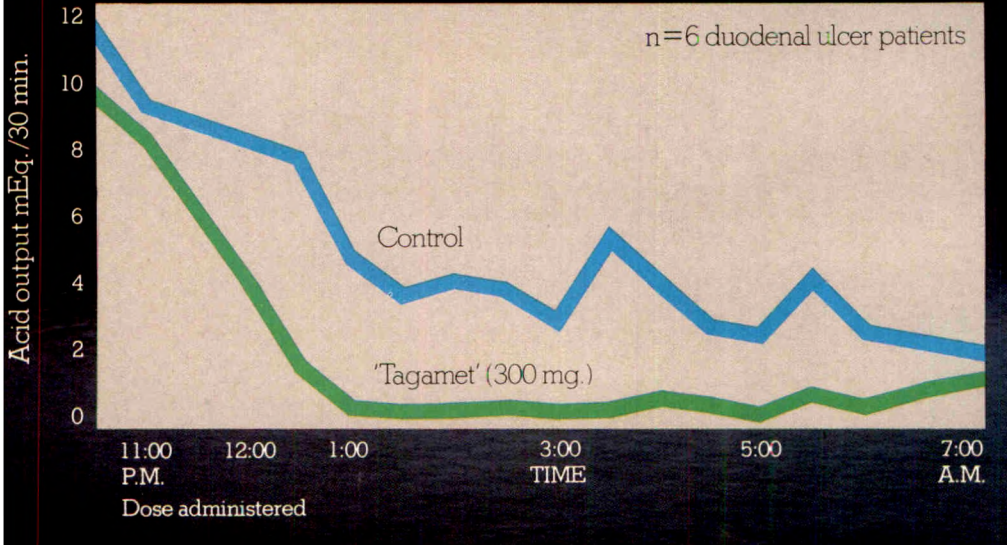
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Working directly at the parietal cell, 'Tagamet' suppresses gastric acid secretion when it matters most– after meals and throughout the night.

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References

1. Richardson, C.T., et al. Gastroenterology 71 (1): 19-23 (July) 1976.
2. Longstreth, G.F., et al. New England J. Med. 294:801-804 (Apr.) 1976.

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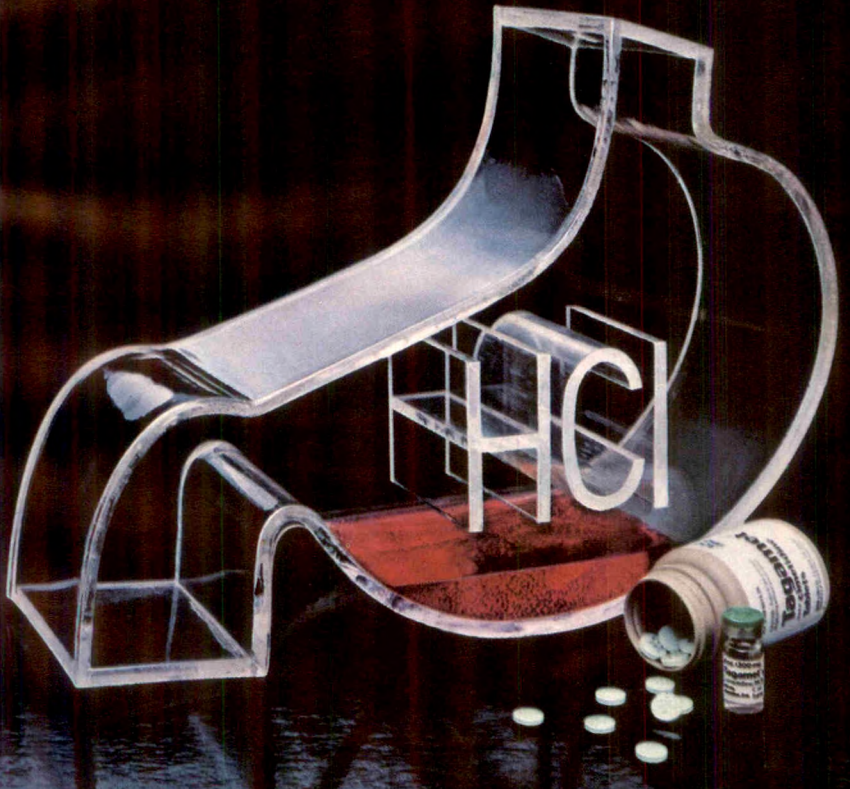
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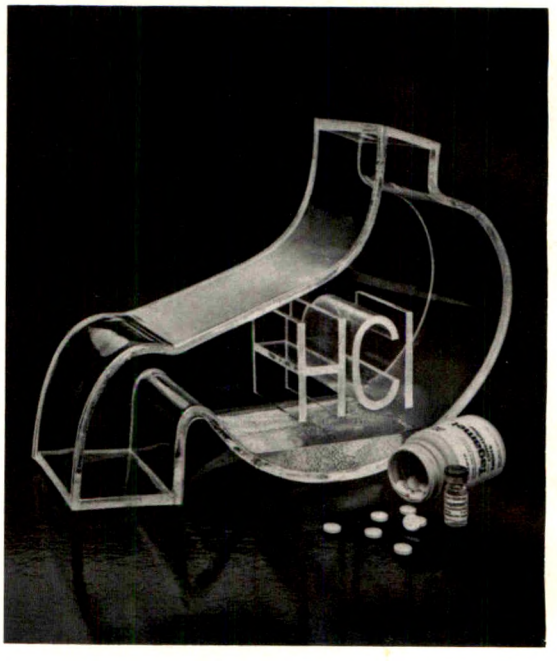
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Effective duodenal ulcer therapy through significant gastric acid suppression.

In *Duodenal Ulcer,* the recommended dosage is 300 mg. four times a day, with meals and at bedtime. Treatment periods should not exceed eight weeks.

While healing may occur during the first week or two, 'Tagamet' therapy should be continued for four to six weeks unless healing has been demonstrated by endoscopic examination.

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Concomitant antacids should be given as needed for relief of pain.

Dosage should be reduced in patients with impaired renal function.

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

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Contraindications: There are no known contraindications to the use of 'Tagamet'.

Precautions: In a 24-month toxicity study in rats at dose levels approximating 9 to 56 times the recommended human dose, benign Leydig cell tumors were seen. These were common in both the treated and control groups, and the incidence became significantly higher only in the aged rats receiving 'Tagamet'. Reproduction studies in animals have shown no evidence of impaired mating performance or fertility.

Lack of experience to date precludes recommending 'Tagamet' for use in pregnant patients, women of childbearing potential, nursing mothers or children under 16 unless anticipated benefits outweigh potential risks; generally, nursing should be discontinued in patients taking the drug.

Adverse Reactions: Diarrhea, muscular pain, dizziness, rash, mild gynecomastia. A few cases of neutropenia have been reported, but no causal relationship could be established. Small, regularly observed, reversible increases in plasma creatinine and some increases in serum transaminase have been reported.

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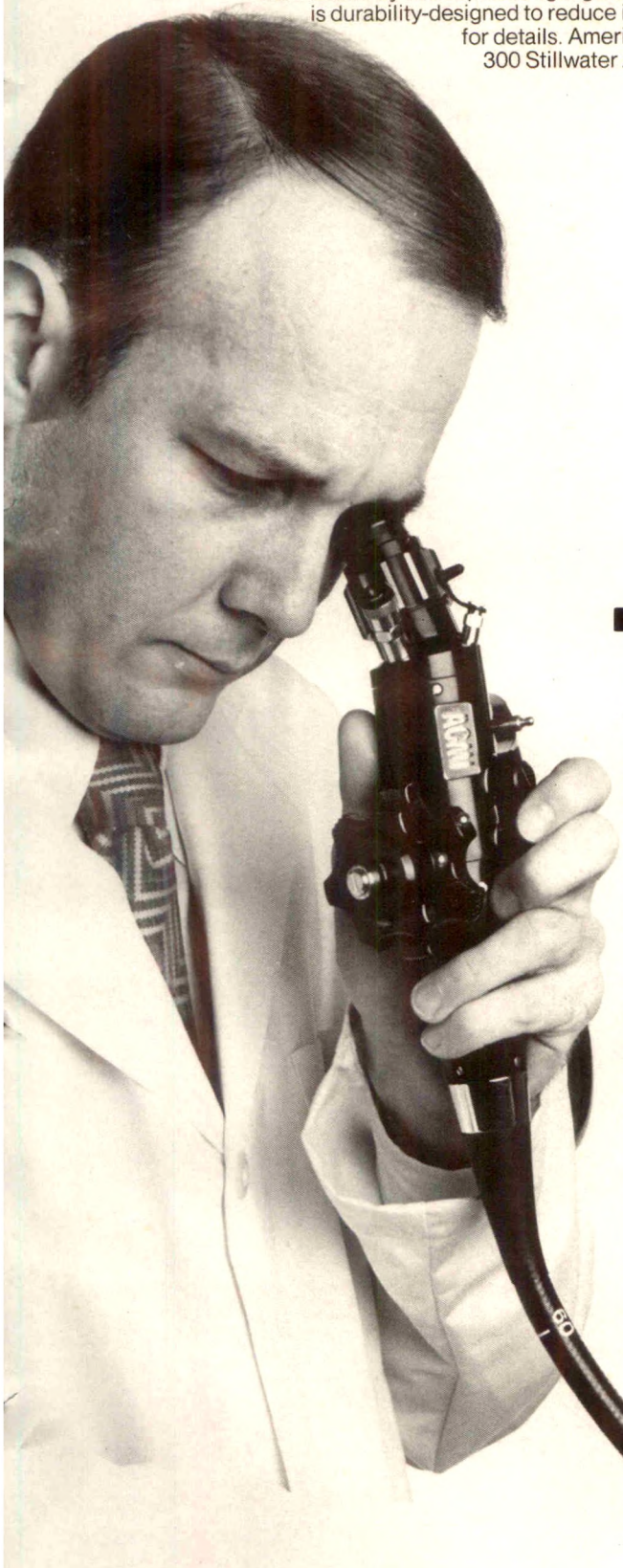
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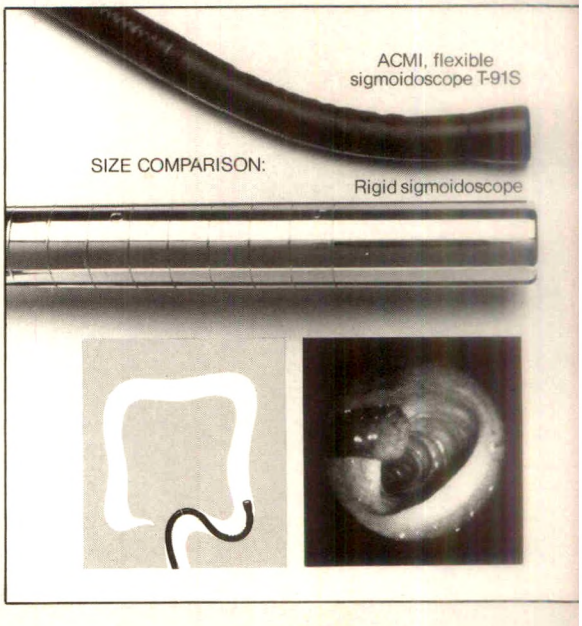
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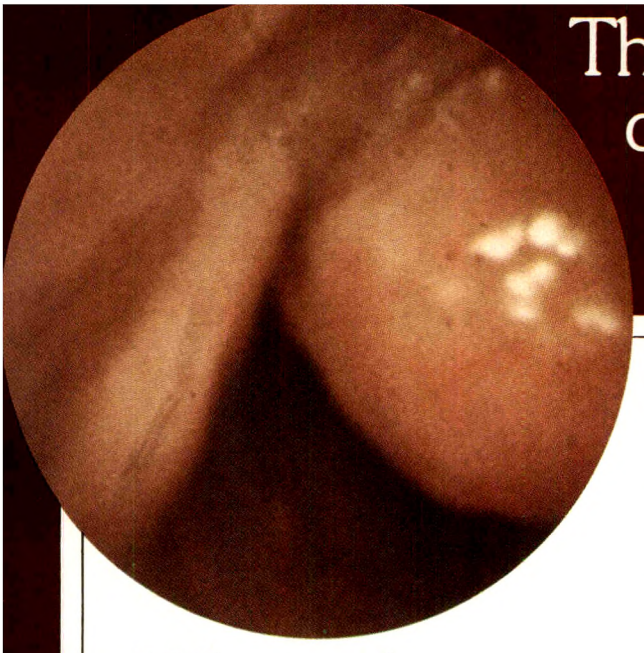
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The patient has dysphagia of 1½ years' duration.

Physical exam is unrevealing.
X-ray studies are inconclusive.

What is the diagnosis?

Esophagoscopy resolves the question.

A 56-year-old man was seen because of increasingly severe dysphagia of one and a half years' duration. At the time of admission, the patient could take only liquids. Physical examination was unrevealing.

A filling defect of the midesophagus was observed by the radiologist. On several projections it appeared to be extrinsic, although an intrinsic lesion, such as leiomyoma, could not be excluded.

Esophagoscopy was performed, and a round submucosal tumor thought to be a *leiomyoma* was identified at the level of 28 cm from the incisor teeth. The patient refused surgical intervention.

Causes of dysphagia may include esophageal carcinoma, achalasia, lower esophageal ring or esophageal web, as well as benign neoplasm. Benign tumors are rare and when detected are usually only incidental findings. Such tumors may, however, become symptomatic upon reaching a large enough size. Such tumors are most often *leiomyomas*, which can partially obstruct the esophageal lumen. Characteristically, they develop central ulceration and hemorrhage.

Case discussion based on *The Clinical Significance of Esophagoscopy* by Bernard M. Schuman, M.D., one in a series of monographs made available by Roche Laboratories in fulfillment of its commitment to continuing education in gastroenterology. This case history illustrates the diagnostic use of endoscopy; it does not represent an indication for Librax therapy.

Endoscopy

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a valuable aid in the diagnosis of G.I. disorders

The development of highly specialized fiberoptic endoscopes has significantly enhanced the accuracy and efficiency of gastrointestinal diagnosis and treatment. Frequently, when both x-ray and laboratory tests have been repeatedly negative, endoscopy has uncovered an organic lesion.

Whether a G.I. condition is eventually confirmed as functional or organic, every patient should receive a thorough examination of his emotional profile and life stresses; such factors may give rise to the patient's symptomatic complaints or aggravate the symptoms of an organic disorder.

Librax®: a valuable aid in the treatment of irritable bowel syndrome*

The diagnosis of irritable bowel syndrome is based on the patient's symptoms and history, plus the exclusion of an organic disorder. In this condition, Librax has been found doubly valuable as an adjunct to reassurance and counseling because it relieves distressing symptoms of both emotional and somatic origin.

1 Only Librax provides the specific antianxiety action of Librium® (chlordiazepoxide HCl), in addition to the antisecretory-antispasmodic actions of Quarzan® (clidinium Br)—both original developments of Roche research.

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Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Physical and psychological dependence rarely reported on recommended doses, but use caution in administering Librium® (chlordiazepoxide HCl) to known addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions) reported following discontinuation of the drug.

Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.**

As with all anticholinergics, inhibition of lactation may occur.

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established.

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Dosage: Individualize for maximum benefit. Usual maintenance dose is 1-2 capsules, 3-4 times/day, before meals and at bedtime. Geriatric patients—see Precautions.

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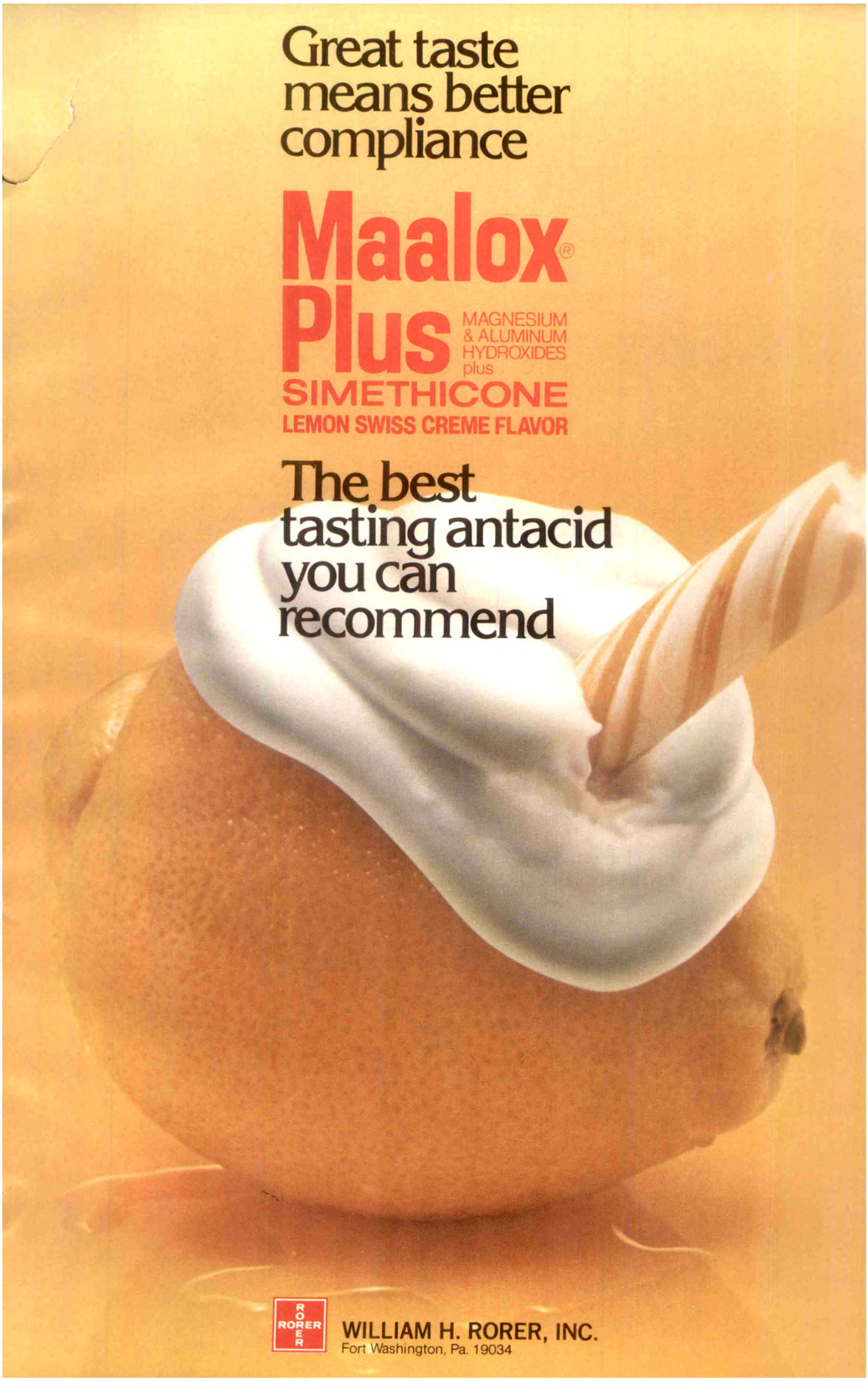
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4½ times greater relapse rate for non-Azulfidine-treated patients revealed in a double-blind study.[1]

Your patients need your guidance to help prevent recurrence of ulcerative colitis. They may not be aware that U.C. with all its pain and discomfort is a chronic disease. Several investigators[2-6] have shown that the best way to control relapse is to medicate over the long-term with Azulfidine (sulfasalazine, N.F.). Further proof is contained in the double-blind "Truelove" study.[1]*

Ulcerative colitis patients were symptom-free at the start of this controlled study. All had been maintained on Azulfidine for from one to over five years. During the six-month trial, more than 54% of the placebo group suffered relapse—a rate 4½ times greater than the 12.1% who showed a recurrence of symptoms in the Azulfidine-treated group! The therapeutic action of Azulfidine was credited with the striking difference in these figures.

The only side effects among the study group were two cases of nausea and one of headache. (These symptoms ceased without a change in dosage when patients returned to open therapy.)

The authors concluded that maintenance treatment of ulcerative colitis with Azulfidine should be continued indefinitely unless contraindicated by side effects. Observe patients carefully, since in many cases adjustment of dosage will control side effects (see Prescribing Information). Azulfidine is also available in enteric-coated EN-tab® tablet form for those patients susceptible to gastric upset.

Over the long haul the best preventative is the proven safety of continuing maintenance treatment.

*Reprint available from Pharmacia.

AZULFIDINE®

(sulfasalazine, N.F.)

Simulated flares on a pipeline intended to represent acute exacerbation of chronic ulcerative colitis.

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(sulfasalazine, N.F.)
Tablets and EN-tabs®

INDICATIONS: AZULFIDINE (sulfasalazine, N.F.) is indicated in the treatment of mild to moderate ulcerative colitis, and as adjunctive therapy in severe ulcerative colitis. AZULFIDINE EN-tabs are particularly indicated in patients who experience gastrointestinal intolerance after the first few doses of the drug, when such intolerance is not primarily due to high blood levels of sulfapyridine and its metabolites and in those for whom a reduction in dosage does not alleviate the gastrointestinal effects.
CONTRAINDICATIONS: Hypersensitivity to sulfonamides or salicylates. In infants under 2 years. Intestinal and urinary obstruction. Pregnancy at term and during the nursing period. In patients with porphyria.
WARNINGS: The safe use of sulfonamides in pregnancy has not been established. Evaluate benefit to risk carefully when giving sulfonamides during pregnancy, especially at term, since kernicterus may be produced in the newborn. The teratogenic potential of most sulfonamides has not been thoroughly investigated in any species and a significant increase of cleft palate and other bony abnormalities has been observed when certain sulfonamides were given orally to pregnant rats and mice at 7 to 25 times the human therapeutic dose.

Deaths associated with the administration of AZULFIDINE (sulfasalazine, N.F.) have been reported from hypersensitivity reactions, agranulocytosis, aplastic anemia, other blood dyscrasias, renal and liver damage, irreversible neuromuscular and CNS changes and fibrosing alveolitis.

The presence of clinical signs such as sore throat, fever, pallor, purpura, or jaundice may be indications of serious blood disorders.

Complete blood counts as well as urinalysis with microscopic examination should be done frequently.
PRECAUTIONS: Administer with caution to patients with impaired renal or hepatic function, severe allergy or bronchial asthma.

Patients with glucose-6-phosphate dehydrogenase deficiency should be observed closely for signs of hemolytic anemia.

Maintain adequate fluid intake to prevent crystalluria and stone formation.
ADVERSE REACTIONS: Adverse reactions have been observed in 5 to 55% of patients included in clinical studies reported in the literature. Experience suggests that with daily dosages of 4 g or more, adverse reactions tend to increase. The most common adverse reactions associated with AZULFIDINE therapy are anorexia, nausea, vomiting, and gastric distress. The following adverse reactions have been reported to occur during therapy with AZULFIDINE.

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Gastrointestinal reactions: Anorexia, nausea, emesis, abdominal pains, diarrhea, bloody diarrhea, impaired folic acid and digoxin absorption, stomatitis, pancreatitis, and hepatitis.

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MEETINGS OF INTEREST

44th Annual Convention, American College of Gastroenterology, Disneyland Hotel, Anaheim, CA, 22-24 October 1979.

Annual Course in Postgraduate Gastroenterology, American College of Gastroenterology, Disneyland Hotel, Anaheim, CA, 25-27 October 1979.

International Conference on Digestive Diseases, Postgraduate Course co-sponsored by the American College of Gastroenterology, the University of South Florida Medical School in Tampa and the Florida Hospital in Orlando. Dutch Inn, Lake Buena Vista, FL, 28-30 January 1979.

IN COMING ISSUES

Papers presented before the 43rd Annual Convention of the American College of Gastroenterology.

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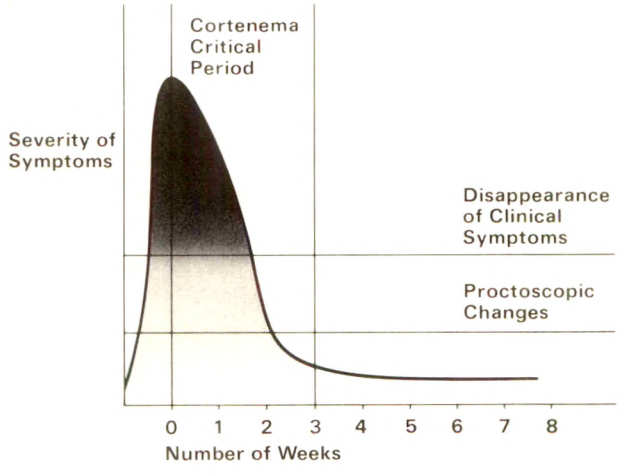
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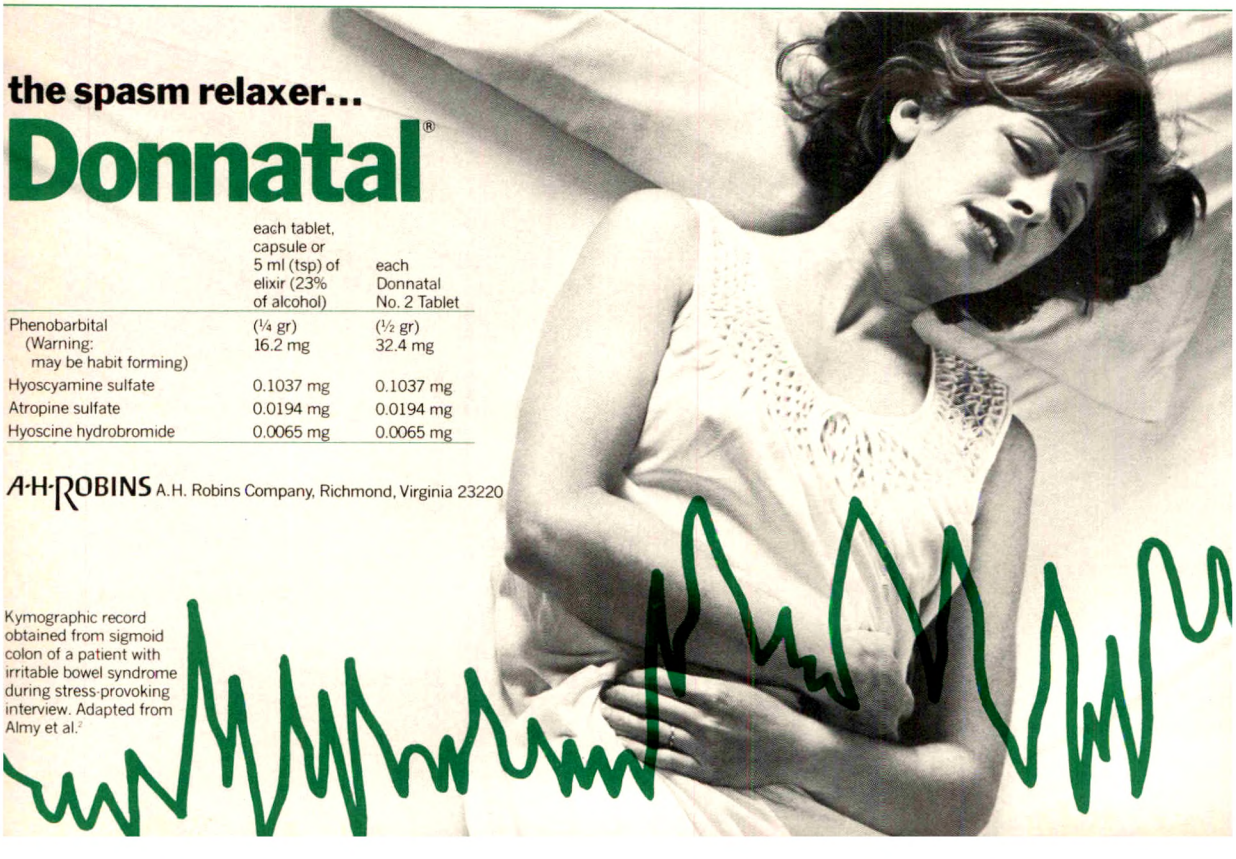
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Kymographic record obtained from sigmoid colon of a patient with irritable bowel syndrome during stress-provoking interview. Adapted from Almy et al.[2]

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Cytological Diagnosis of Digestive Cancer*

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In this paper we will endeavor to describe the present status of the cytological diagnosis of cancer of the digestive tract, based on a review of the current literature as well as our own experience dating from 1952 when Dr. V. Cabre-Fiol established a gastrointestinal cytology laboratory in the Gastroenterology Service of the Hospital Santa Cruz y San Pablo.[1-3]

METHODS

The first efforts of gastrointestinal cytodiagnosis technics were focused mainly on the esophagus and stomach, using washings, abrasive balloons, small sponges and different types of brushes introduced either blindly or under fluoroscopic control.[2] During the past few years most cytologic studies have been done by means of flexible endoscopes permitting sampling of the esophagus, stomach, duodenum, colon and cannulation of the biliary and pancreatic ducts.

For endoscopic cytodiagnosis a variety of instruments have been employed. The following methods are in use: 1. Direct washing of the suspicious lesion, either with isotonic or mucolytic solutions. 2. Direct abrasion by means of nylon brushes.

Direct washings have yielded excellent results according to Kasugai and Kobayashi.[4] They may have a special indication in extensive mucosal lesions in which brushing may be imprecise or in stomachs with large folds or multiple polyps.

Endoscopic abrasion is a simple and rapid method which allows sampling of large areas under visual control. It is the preferred method in most endoscopic centers. Most endoscopists use the standard brushes provided by the manufacturers. The material obtained can be smeared directly on slides or immersed in saline and centrifuged. Our own results have been better with the latter technic. When different lesions require study during the same examination, we strongly recommend the use of a different brush for each lesion.

The Papanicolaou and the May-Grunewald-Giemsa stains are still the two most extensively used for slide preparation and the criteria for malignancy used are those classically described by Papanicolaou.[2]

CYTOLOGY OF THE ESOPHAGUS

The usefulness of esophageal cytology by either lavage procedures or abrasion has

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TABLE I

CYTOLOGIC DIAGNOSIS OF ESOPHAGEAL CANCER

Author	Method	No. of cancer cases	Per cent positives
Honan physicians[5]	Blind abrasion	3,768	87.8
Gephart and Graham[6]	washings	89	73.0
McDonald, et al[7]	washings	72	68.0
Bemvenuti, et al[8]	endoscopic brush	64	87.5
Halter, et al[9]	endoscopic brush	11	81.8
Prolla, et al[10]	endoscopic brush	73	89.0
Hospital San Pablo	blind abrasion	111	92.0
Hospital San Pablo	endoscopic brush	239	96.2

been well established. The largest series of early cancer diagnoses may well be that of the Chinese workers in the Honan province,[5] who used a rubber tube to which a little abrasive balloon was attached. In the last few years, the frontal view endoscope, which allows cytologic studies by means of washings or exfoliation through brushes under visual control, has become the instrument of choice. Both technics should be performed before biopsy which might interfere with cytological sampling. In Table I the results of esophageal cytology are presented. False positives are rare in cytologic laboratories with extensive experience. They are usually less than 2%. Abnormal cells may exfoliate from areas of severe esophagitis or from the edges of esophageal ulcers. In our experience with endoscopic cytology we have not yet made false positive diagnoses of esophageal cancer (Table I).

Esophageal cytodiagnosis may be difficult in extensive necrotic and/or hemorrhagic lesions or in cases with mycotic infections secondary to esophageal obstruction. Cytologic characteristics of squamous carcinoma, however, are usually prominent and render the diagnosis easy, as other authors, reporting high accuracies, have repeatedly confirmed.[6-10] Diagnosis may be more difficult in adenocarcinomatous lesions which might grow submucosally. In stenotic lesions small brushes may be used with great advantage.

Early esophageal cancer has been occasionally diagnosed by means of abrasion. The Chinese experience, which started in 1961, is most impressive and has shown the applicability of cytology to the screening of large rural populations. In general, early cancer of the esophagus has not been diagnosed often. Nabeya and Takigawa reviewed the Japanese experience in 1975 comprising 58 cases. About 16% of them were still at the intraepithelial stage and 5% reached the *muscularis mucosae*. The rest (79%) invaded the submucosal layer. Seifert, et al[12] have published the first report of early cancer of the esophagus diagnosed by endoscopic cytology. Another case has been reported by Belladonna, et al. [13] We have seen only two cases of early cancer. One of them was diagnosed by blind abrasion and the second by endoscopic brushing, later confirmed by biopsy. Both were epidermoid tumors.

TABLE II

ENDOSCOPIC CYTOLOGIC DIAGNOSIS OF GASTRIC CANCER

Authors and methods	No. of cases	Per cent positives	Per cent false positives
Washings:			
Kasugai and Kobayashi[4]	512	96.0	2.0
Ishioka, et al[15]	278	92.8	0.9
Brushing:			
Kasugai and Kobayashi[4]	73	87.6	—
Bemvenuti, et al[8]	71	85.9	3.8
Weidenhiller[35]	116	90.5	4.3
Winawer, et al[36]	50	68.0	—
Halter, et al[9]	39	84.6	0.0
Prolla, et al[10]	110	81.8	0.7
Hospital San Pablo	515	92.2	1.1

CYTOLOGY OF THE STOMACH

Endoscopic cytology through the fiberscope has largely superseded other procedures. The results of gastric endoscopic cytology are presented in Table II.

EARLY GASTRIC CANCER

The greatest problem in gastric cancer diagnosis is still the fact that many lesions are diagnosed at an advanced stage. The usefulness of early diagnosis has been largely demonstrated in Japan, where Hayashida and Kidokoro[14] reviewed 365 cases from 22 different institutions. Five-year survival was 92.5%. According to Ishioka, Yamagata, et al[15] metastases are exceptional in this type of lesion; even in cases with positive perigastric lymph nodes survival may be as high as 90%. Early cancer seems to originate in the lower part of the gastric foveolae, particularly in the pyloric mucosa where regenerative changes are most often observed.[16]

TABLE III

ENDOSCOPIC CYTOLOGY OF EARLY GASTRIC CANCER

Authors	No. of cases	Per cent positives
Kasugai and Kobayashi[4]	128	95.3
Ishioka, et al[15]	339	95.6
Prolla, et al[10]	5	100.0
Serck-Hansen, et al[23]	11	72.7
Hospital San Pablo	10	90.0

The possibilities of cytodiagnosis are here equal to those reported in advanced cancer. In our own experience, based on 16 cases of early carcinoma diagnosed either by endoscopic cytology (10 cases) or previously by abrasion and washings (6 cases), we have never been able to find any differential cytologic criteria which would have permitted the diagnosis of early cancer as compared with the ordinary type of advanced carcinoma. The results of cytology in early cancer are shown in Table III.

NONEPITHELIAL GASTRIC MALIGNANCIES

The first cytologic diagnoses of gastric lymphoma were reported by Rubin and Massey[17] in 1954. With increased experience, the various types of lymphoma (histiocytic, lymphocytic, Hodgkin's disease) can be differentiated occasionally.[18] Recently, the cytologic diagnosis of gastric leiomyosarcoma has been made.[19] The cytologic diagnosis of gastric plasmocytoma has

TABLE IV

CYTOLOGIC DIAGNOSIS OF GASTRIC LYMPHOMA

Authors	Method	No. of cases	Per cent positive
Rubin and Massey[17]	Washings	4	75.0
Prolla, Kirsner[26]	Washings	42	64.2
Hospital San Pablo	Abrasion,	17	41.1
	endoscopic brushing	15	86.6
Kline, Goldstein[37]	Washings	9	77.7
Prolla, et al[18]	Endoscopic brushing	13	76.9
Bemvenuti, et al[8]	Endoscopic brushing	9	88.8

also been reported.[20] The over all results of cytology are shown in Table IV. The accuracy of diagnosis using endoscopy sampling methods seems to be greater than that obtained with blind technics.

CYTOLOGY OF THE PANCREAS

The main problem in pancreatic cytology is that of obtaining an adequate washout of the ducts to allow malignant cells to exfoliate into the duodenal lumen carried by the stimulated pancreatic juice. Intravenous secretin has been used for this purpose, usually in dosage of 1 U./kg. The stimulation of endogenous secretin by instillation of 100 ml. of a 2/1,000 solution of hydrochloric acid has also been used in our laboratory. The response is usually less than with intravenous secretin but it has the advantages of its innocuousness and inexpensiveness.[21] In recent years, cannulation of the ampulla of Vater through the fiberscope has permitted the obtaining of pure pancreatic juice. The procedure, at least experimentally, seems to involve little risk.[22] Secretin may also be administered at the time of cannulation. This, however, adds to the hazard of cannulation that of the administration of secretin. To obtain adequate material, some authors have to aspirate pancreatic secretion for quite a long time, sometimes several hours. Brushing of the pancreatic duct has been done by Norwegian workers with good results reaching 75% of positive diagnoses.[23] Again, time will tell whether this is the procedure of choice and whether intraductal brushing is a safe procedure. Obviously lesions at the body and tail of the pancreas may be difficult to reach by endoscopic brushing. To judge from the results reported in the literature (Table V) there is still no procedure of choice for the cytologic diagnosis of pancreatic cancer. Most reported series are too small to provide a definitive answer. Cytologic aspiration of the pancreas at laparotomy by means of a fine needle has allowed confirmation of carcinomatous changes in 34 of 36 cases.[24]

CYTOLOGY OF THE BILE DUCTS

Duodenal drainage, using either magnesium sulfate (33/100 solution), olive oil, or more recently, cholecystokinin pancreozymin, may provide a cytological diagnosis of cancer of the extrahepatic bile ducts and of the gallbladder. Malignant cells are usually found isolated or in small clumps. They often can be recognized as cells from columnar epithelium often associated with heavily pigmented bile secondary to bile retention.

TABLE V

CYTOLOGIC DIAGNOSIS OF PANCREATIC CANCER

Authors	Method	No. of cases	Per cent positives
Prolla and Kirsner[26]	Duodenal drainage	156	57.6
Goldstein and Venteke[38]	Duodenal drainage	24	75.0
Ishioka[39]	Duodenal drainage	81	42.0
Hospital San Pablo	Duodenal drainage	40	45.0
Endo, et al[40]	ERCP	29	79.0
Hatfield, et al[41]	ERCP	26	53.0
Serck-Hansen, et al[23]	ERCP (brushing)	29	75.0

Henning, et al[25] have reviewed the over all results of the cytological diagnosis of cancer of the bile ducts (Table VI). Although they do not report their own results, their experience did not seem to be very optimistic. Among 350 benign lesions a total of 2.8% false positive results were found. At the University of Chicago, among 1,999 cases with benign lesions studied between 1956-1968, the number of false positives was only 0.5%.[26] Our own results, from 1953-1969, are very similar. Kimura, et al[27] have reported 0.6% false positive diagnoses among 314 benign conditions.

CYTOLOGY OF THE COLON

Colonic cytodiagnosis may be done by abrasion of the lesion under visual control or by blind washings. The direct method had the disadvantage of the limited reach of the sigmoidoscope, although occasionally a positive cytologic diagnosis could be made by collecting through the sigmoidoscope secretions originating in more proximal lesions. Blind washings, as done by Raskin and Pleticka[28] had the disadvantage

TABLE VI

CYTOLOGIC DIAGNOSIS OF BILIARY TRACT CANCER

Authors	No. of cases	Per cent positives
General review Henning, et al[25]	181	63.0
University of Chicago Prolla and Kirsner[26]	18	50.0
University of Sendai Kimura, et al[27]	30	40.0
Hospital San Pablo	15	46.0

of being time-consuming, uncomfortable for the patient and, in general, of giving a lower yield than the cytologic diagnosis at other sites. The use of the fiberscope has allowed, as in other areas of the gut, direct sampling of the suspicious lesions either by washings or brushing technics. Cytologic brushing has been used extensively on our service since 1971. The results of colonic cytology are shown in Table VII. False positive results are few. Raskin and Pleticka report about 2.0%; Rachail, et al[29] only 0.4%. We have seen only one false positive case in a patient with Crohn's disease of the colon. Bizarre cells with abnormal nuclei are sometimes seen in ulcerative colitis which can be troublesome from the diagnostic point of view.

Bemvenuti, et al[8] have studied four patients with ulcerative colitis and carcinoma. No false positive diagnoses were made and the combination cytology-biopsy attained an accuracy in the whole series of 96.0%. In our own experience, cytology combined with biopsy provided 96.5% positive diagnoses, while biopsy alone gave 86.3% positive results. Most of the lesions we have studied were carcinomas made of columnar type cells. In three cases the cells had epidermoid characteristics. Another case was diagnosed as lymphocytic lymphoma. Kline and Yum[30] have been

TABLE VII

CYTOLOGIC DIAGNOSIS OF COLONIC CANCER

Author	Method	No. of cases	Per cent positives
Prolla and Kirsner[26]	Colonic lavage	112	77.6
Kline and Yum[30]	Endoscopic lavage	34	70.0
Bedine and Cocco[42]	Endoscopic brush	42	97.6
Rachail, et al[29]	Endoscopic brush	86	86.0
Bemvenuti, et al[8]	Endoscopic brush	23	82.7
Hospital San Pablo	Endoscopic brush	281	92.5

able to make a positive diagnosis in six cases of early cancer of the colon.

Brushing may allow adequate cytologic sampling beyond stenotic areas in which biopsy may be impossible to perform. Cytology may have special indications in the study of anastomoses after colonic resection for carcinoma and in long standing cases of chronic inflammatory colonic disease in which malignant changes may occur. In these instances, colonic washings under visual control might be the method of choice.

THE PLACE OF CYTOLOGY IN THE DIAGNOSIS OF DIGESTIVE CANCER

In recent years, cytology has gained widespread acceptance as a diagnostic technic, mostly as a complement to endoscopic biopsy. This is particularly so in special instances, such as stenotic lesions of the esophagus and the colon in which biopsy is not technically feasible and in the diagnosis of early cancer for which it might be necessary to sample wide areas of the mucosa. The ultimate value of cytology in the diagnosis of more conventional lesions, however, has not been fully ascertained. In experienced laboratories in which false positive diagnoses are kept to a minimum, cytology has proven to be a procedure with a high sensitivity (percentage of true positive diagnoses among cases with a positive cytology), a very high specificity (percentage of negative reports among the total number of true negative cases) and consequently, a very high efficiency (percentage of both positive and negative cases correctly classified as such).[31, 32] In our own laboratory, sensitivity and efficiency run about 90.0% in the diagnosis of esophageal, gastric and colonic cancers. Cancer of the pancreas is diagnosed cytologically with a much lower efficiency (about 75.0%), somewhat better than the figures recently obtained at the Mayo Clinic[33] in a prospective study. The reason for this is that the sensitivity of the test is quite low, less than 50.0%, while specificity is very high (no false positive in our series). Unfortunately, in many reports in the literature, this information is not available, perhaps because of difficulties in the follow-up of the cytologically negative cases.

In spite of the impressive achievements of cytology, many gastroenterologists seem to believe that the opportunities for this procedure to contribute to a positive diagnosis of cancer are few. They rely mainly on biopsy studies, even if their results, which sometimes are equally impressive, are often lower than those of cytology.[34]

Cytology laboratories cannot be improvised. The technic is often time-consuming although direct sampling of the lesions now provides much more abundant material than does the use of blind technics. The cost efficiency of cytology in gastrointestinal cancer has not been evaluated yet. The next few years will probably decide whether cytology is a truly advantageous technic for routine work or only a procedure to be

restricted to the investigation of patients in whom biopsy studies have been negative.

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Communication from Abroad

Enterostomy in Patients with Primary Neuropathic Amyloidosis

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Three patients with primary neuropathic amyloidosis are reported. They were all almost totally disabled by either diarrhea and *incontinentia alvi* or obstipation. In all three patients enterostomies were tried as a palliative treatment and the results of the operations have been very promising.

Introduction

Primary neuropathic amyloidosis (PNA) is a severe metabolic disease with obscure pathogenesis and a spotted geographical distribution. A well known form of PNA is the Portuguese type, which is mainly found among fishermen in northern Portugal. The inheritance is a Mendelian autosomal dominant trait and thus far 173 families have been identified.[1-3] The chief manifestations of PNA are neuropathy of peripheral and autonomic nerves. Various gastrointestinal symptoms, micturition problems, impotence, anhydrosis due to disturbances of autonomic nervous function are often seen in these patients.[1-7] This disease has been reported in patients, some of whom are of Portugese descent, in several other countries as well, including the United States,[8-10] England,[11] Germany,[12] Brazil[13] and Sweden.[14, 15] A rather similar syndrome has been reported from Japan.[16] The genetic and geographic points in the different syndromes of amyloidosis have been extensively reviewed by Thomas.[17]

PNA has been reported from northern Sweden by Andersson.[14, 15] His material consisted of 60 patients and of these, 42 belonged to 15 families, while the rest had no known heredity. These patients very often have disturbances of the gastrointestinal tract. Obstipation is often the first symptom. Later on there are periods of intense diarrhea. Pronounced diarrhea, sometimes associated with *incontinentia alvi*, was present in 21 patients.

The prognosis of PNA is *quo ad vitam* poor and especially poor in the cases with severe diarrhea.[14, 15] It is probable that a complicating malabsorption, which frequently is diagnosed, is the cause for this difference in survival. Profuse diarrhea, in combination with *incontinentia alvi*, means a tremendous physical and social handicap. It should be noted that cerebral function is quite well preserved even in later stages of the disease.

Surgery in a patient with advanced peripheral neuropathy, diarrhea, malnutri-

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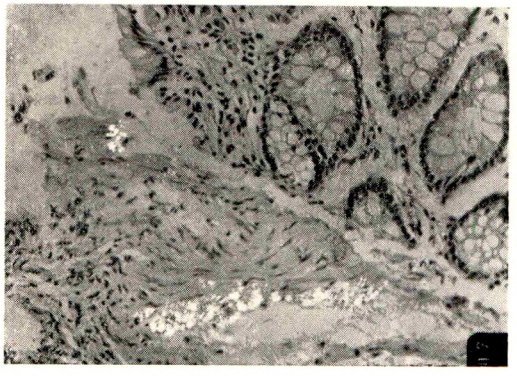


Fig. 1—Section from the colonic mucosa of Case 1. In polarized light, tissue containing amyloid substance appears bright green (white in the photomicrograph). The amyloid substance is mainly found in the walls of small vessels. Alkaline congo red stain and polarized light. Courtesy of Roger Stenling M.D., Department of Pathology, University of Umea.



Fig. 2—Section from the colonic mucosa of Case 1. The amyloid substance is located in small vessels beneath the *muscularis mucosae*. Alkaline congo red stain and polarized light. Courtesy of Roger Stenling M.D., Department of Pathology, University of Umea.

tion and disturbances of fluid and electrolyte balance is hazardous. In the University Hospital of Umea, during the last years we have treated three patients with PNA who were almost totally disabled by diarrhea or obstipation. We decided after a great deal of deliberation to try to help them with different types of enterostomies. The results have thus far been so promising that we wish to report them.

Case Reports

Case 1:—G. Q., 39-year old male, former manager of an advertising agency. In 1969 he observed increasing obstipation, impotence and reduced salivation. Primary amyloidosis with pericollagen distribution according to the classification of Heller, et al[18] was verified by rectal biopsy in 1971 (Figs. 1 and 2). At this time there was a sensory loss in the feet and lower legs. Periods of explosive diarrhea occurred. From 1971-1975 the polyneuropathy grew worse in all extremities. He also developed severe ortostatism and atony of the urinary bladder. The periods of diarrhea became more and more frequent and eventually he lost control of the anal sphincter. From the beginning of 1975 he was incapable of going outdoors and spent most of his time in the lavatory.

The conditions of life for the patient and his family became completely unbearable and enterostomy was discussed as a possible solution. On examination we found a pale, thin man (total weight loss 20 kg. since the debut). Blood pressure 100/75 mm. Hg. There was pronounced wasting of the musculature in the feet and lower legs. There was a moderate atrophy of the thenar muscles but he was capable of handling the ostomy appliances that we intended to use. He had steatorrhea, 10.6



Fig. 3—A barium enema just before the operation of Case 2. No gross anatomical changes could be detected.

gm. fat/24 hours and an abnormal d-xylose tolerance test. Hemoglobin was 139 gm./l. Albumin in the serum was 35 gm./l. After a short period of preoperative preparation with parenteral fluid, albumin and electrolytes he was operated upon in March, 1975. We made a short end sigmoidostomy. The aboral part of the sigmoid colon was closed and replaced into the pelvis. No abnormalities were found in the abdominal cavity. The postoperative course was uneventful. He learned to handle the necessary appliances very soon and left the hospital after 10 days. His hands are weak because of progression of the neuropathy but today, 20 months after the operation, he can leave his house, even go abroad and also do some work in his advertising office. He has still his periods of "diarrhea", which, however, causes little trouble.

Case 2:—G. B., 42-year old former postwoman. In 1967 she noted paresthesias and pain in the lower legs and in 1971 loss of sensibility below the knees. The diagnosis, amyloidosis was made in 1972 when amyloid with pericollagen distribution was found in rectal biopsy specimen. In 1973 she began to have gastrointestinal disturbances, mainly in the form of obstipation. There was also a slow progress of her polyneuropathy. From December, 1975 the obstipation became very severe. The stools were passed every third week (sic!) and then only after intense treatment with bulk-laxatives, enemas, neostigmin, etc. She had gone through two painful deliveries but described every evacuation of the bowels as more troublesome than those. She was hospitalized every third week and narcotic drugs were needed to overcome the abdominal pain which accompanied a successful evacuation of the bowel. In this situation the question of enterostomy came up after a long period of hesitation and discussion between physicians and surgeons.The patient pressed for an operation. In May, 1976 she was admitted for surgery. She was pale and weighed 52 kg. (total weight loss since debut 12 kg.). There was also atrophy and loss of sensibility in the feet and lower legs as well as a loss of the fine motor functions of the hands. Hemoglobin was 141 gm./l., albumin was 39 gm./l. and she had a pathological d-xylose tolerance test. Following a barium enema (Fig. 3), a conventional ileostomy was made. The aboral part of distal ileum was closed and replaced into the abdominal cavity. No gross abnormality, that could explain her severe obstipation, was found when the abdomen was explored during the operation. The postoperative course was uneventful. After 10 days she left the hospital and was able

to handle the ostomy appliances without any help. Today, 10 months after the operation, she has gained 2.5 kg., she has no abdominal pain. She has been able to spend about two and a half months in the Canary Islands. In spite of some progression of the polyneuropathy in the hands she is still fully capable of handling the ostomy and the appliances herself.

Case 3:—R. A., 45-year old male, a former joiner. In 1967 he started to have paresthesias, pain and weakness in the lower legs. Two years later he lost the sensibility of the lower legs. In 1970 he also noted paresthesias in the fingers and the same year he became impotent. Biopsy specimens from the rectal mucosa showed amyloid substance with pericollagen distribution. In 1972 he required permanent urinary catheter and the same year a moderate diarrhea appeared. From 1973 the periods of diarrhea became more frequent and severe and the patient lost control of the anal sphincter. From then on he was virtually disabled by his gastrointestinal condition and in the beginning of 1975 a permanent hospitalization was discussed (he was divorced at the time). The polyneuropathy had progressed and he was unable to close buttons. In this situation an enterostomy seemed to be the only possible help we could offer the patient. Before the operation he was in serious condition. Body weight was 52 kg. (total weight loss during the illness 22 kg.). He had a slight hypostatic edema. Albumin in serum was 34 gm./l. Hemoglobin was 117 gm./l. There was also steatorrhea (14.7 gm. fat/24 hr.) but a normal d-xylose tolerance test. The electrocardiogram showed a atrioventricular block of the second degree. In April, 1975 a short end sigmoidostomy was performed. The aboral end of sigmoid colon was closed and replaced into the abdominal cavity. The postoperative course was uneventful and after 12 days he left the hospital fully capable of managing the appliances himself. In spite of some progress of the polyneuropathy, especially in the right hand, he is still able to handle the ostomy and its appliances 18 months after the operation. He has gained 4 kg. and it is possible for him to get about outdoors and visit friends in distant places.

Comment

Gastrointestinal symptoms are common features of PNA. They consist mainly of obstipation and/or diarrhea. Gastric emptying is often delayed and at times vomiting can be a great problem. These symptoms are most probably due to amyloid infiltration of the autonomic nervous system since no gross anatomic changes have been detected.[14, 15, 19] The malabsorption syndrome has been shown to be rather common in the Swedish patients with PNA.[15] Of 31 patients examined, 18 had steatorrhea.[20] The pathophysiology of this malabsorption is still obscure and has to be investigated further. Other clinical manifestations that are described in gastrointestinal amyloidosis include peptic ulcerations in duodenum and ventricle,[21, 22] ulcerations of the colon,[23] protein loss,[24] bleeding,[24] obstruction of the intestinal lumen with amyloid masses,[22] pseudo-obstruction, i.e. clinical signs of mechanical obstruction without organic occlusion of the lumen,[25] ischemia of the intestinal wall because of amyloid obstruction of the vasculature,[26] perforations.[27]

Abdominal surgery, in cases of gastrointestinal amyloidosis, has been performed only in a few instances and then only on vital indications such as profuse bleeding, intestinal ischemia or intestinal pseudo-obstruction.[23, 25, 26, 28] As far as we know, there are no reports of elective surgery based on the same indications as in our patients.

Our three patients with diagnosed PNA illustrate that the gastrointestinal dis-

turbances with diarrhea, obstipation and fecal incontinence bring about much suffering and immense social problems in PNA.

The general condition of these patients was so bad that pre- or postoperative complications might have been expected. Our experience was to the contrary, however. The patients tolerated the operations and the immediate postoperative period very well. The unaffected cerebral function in these patients and their strong motivation for the operation may be of great importance for the favorable course of events.

We were also worried that the polyneuropathy in the hands of the patients would create difficulties in handling the ostomy appliances but on the contrary they seemed to learn the technic remarkably quickly.

To these three patients the enterostomy operation meant a new life. Even if the PNA will progress further as there is nothing but symptomatic treatment of the disease available and when the patients eventually will be unable to take care of the ostomy themselves, the enterostomy certainly will facilitate the nursing. Enterostomy operations may also be a valuable palliative measure in other neurological diseases with loss of anal sphincter control.

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Pancreatic Cancer Presenting as Pancreatitis of Pregnancy

CASE REPORT

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Pancreatic cancer was found postmortem in a 37-year old Caucasian female who developed severe and complicated pancreatitis in the last trimester of pregnancy. This association has not previously been reported. This case illustrates the difficulty of diagnosing pancreatic cancer in the setting of significant pancreatic inflammation.

Pancreatitis complicating pregnancy is well recognized,[1-3] although some textbooks of gastroenterology do not comment on this association.[4] Two recent reviews of pancreatitis occurring in pregnancy emphasize that it is rare; it usually occurs in the third trimester or the early puerperium and it may be severe with a mortality of up to 37%. Gallstones, drugs received during pregnancy and lipid abnormalities may play a role in some cases. Alcohol is rarely a factor in this group, and most cases are idiopathic.[1, 2] The following case represents the first report of pancreatic cancer presenting as pancreatitis of pregnancy. This case illustrates the difficulty of diagnosing pancreatic cancer when significant pancreatitis is also present.

CASE REPORT

The patient was a 37-year old Caucasian housewife who had been in excellent health with three previous uncomplicated pregnancies. She had no history of abdominal pain, alcohol abuse, gallstones, trauma, lipid abnormalities, diabetes mellitus, medications during pregnancy or familial pancreatic disease.

In the seventh month of her fourth pregnancy, she developed intermittent nausea, vomiting and epigastric discomfort with meals. She delivered a healthy child at term but had mild icterus and depression. The icterus was at first attributed to cholestasis of pregnancy. Postpartum she continued to have attacks of epigastric pain, nausea and vomiting and she developed inanition and progressive obstructive jaundice. She had a normal serum amylase (106 Caraway units/100 ml., normal, 60-160) and an elevated urine amylase (429 Caraway units/hr., normal, less than 300 C.U./hr.). Six weeks after delivery a laparotomy showed an inflamed and swollen pancreatic head with a distended biliary system containing no gallstones and with a pseudocyst in the tail of the pancreas. A needle biopsy of the pancreas through the duodenal wall showed pancreatitis. A cholecystectomy and choledochoduodenostomy were performed. Pain, vomiting and inability to eat persisted so the patient underwent drainage of the pancreatic pseudocyst into her stomach two months later. Nonetheless,

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she remained symptomatic and also developed frequent fevers. She was transferred to Duke Hospital on 5 August 1975, having lost a total of 27 kg. over 10 months.

On physical examination she was pale, cachectic and febrile without icterus but with mild generalized lymphadenopathy. Her abdomen bore a healed cholecystectomy scar and was tender in the epigastrium. In addition to hepatosplenomegaly she had a deep epigastric mass and an epigastric bruit. Her bowel sounds were normal.

Laboratory findings:—Hematocrit, 35%; white cell count, 9,400/cu. mm.; glucose, 115 mg./100 ml.; calcium, 8.6 mg./100 ml.; phosphorus, 4.1 mg./100 ml.; bilirubin, 0.9 mg./100 ml.; SGOT, 78 I.U.; alkaline, phosphatase, 760 I.U.; amylase, 47 I.U.; cholesterol, 156 mg./100 ml.; carcinoembryonic antigen greater than 20 ng./ml. (CEA-Roche Radioimmunoassay, normal less than 2.5 ng./ml.). A liver scan was normal except for splenomegaly. An ultrasound examination showed a mass in the pancreas consistent with pancreatitis. Abdominal arteriography showed an avascular area in the region of the pancreas which was interpreted as a possible pancreatic abscess and also showed a splenic vein thrombosis.

The patient's hospital course included intravenous hyperalimentation complicated by gram negative sepsis, shock and acute tubular necrosis. She required three additional laparotomies for management of abdominal abscesses. She developed gastrointestinal bleeding from stress ulcers, and she continued to have a febrile and intermittently septic course while on antibiotics. She finally expired on 5 December 1975, 13 months after the onset of her illness.

At postmortem examination, she had acute and chronic pancreatitis with a pancreatic abscess and a pancreatic pseudocyst. In addition, she had an adenocarcinoma of the pancreas with metastases to the surrounding lymph nodes and the liver and spleen.

Comment

Despite several operative procedures on her abdomen and a relentless downhill course, several factors misled us from recognizing the true diagnosis of pancreatic cancer in this case. First, pancreatitis is a rare but recognized complication of pregnancy.[1, 2] Second, pancreatic cancer is uncommon in women of child-bearing age.[5] Third, the diagnosis of pancreatic cancer in the setting of significant pancreatic inflammation is notoriously difficult to make even by laparotomy.[6] Finally, we know of no precedent for pancreatic cancer presenting as pancreatitis of pregnancy.

Dreiling and his associates have studied pancreatic function during pregnancy in dogs. They found that basal pancreatic secretion of water, bicarbonate and pancreatic enzymes are increased in late pregnancy and in the early puerperium. The response to exogenous secretin is relatively unchanged but the response to exogenous cholecystokinin is increased.[7, 8] Translation of observations in dogs to clinical conditions in man is difficult but if the human pancreas is in a similar hypersecretory state during late pregnancy, then this might amplify the pancreatic inflammation in response to a superimposed injurious agent or disease process in the pancreas.

In the present case, detection of the underlying pancreatic cancer was impaired by the amount of associated pancreatic inflammation. Many of the tests for diagnosing pancreatic cancer can be confusing when severe pancreatic inflammation is also present. An elevated level of carcinoembryonic antigen in serum and in pancreatic juice can be seen in both pancreatitis and pancreatic cancer, although the values are

generally higher in patients with cancer.[9-11] A recent review of tests for detection of pancreatic cancer concludes that abdominal ultrasound and pancreatic secretory tests are useful screening tests for the presence of pancreatic disease. Pancreatic cancer in patients with a positive screening test can best be confirmed with an endoscopic retrograde pancreatogram.[12] Others have also emphasized the value of endoscopic retrograde pancreatography in the detection of pancreatic cancer.[13] An advantage of this procedure over other radiologic procedures is that pancreatic juice can also be collected for cytology.[11, 14] Endoscopic retrograde pancreatography was not performed in the present case, however, the results might have been difficult to interpret. Acute and chronic pancreatitis, pseudocysts and pancreatic abscesses all can produce pancreatic ductal obstruction which may be difficult to distinguish from that produced by pancreatic cancer.[15] Abdominal arteriography is almost as effective as endoscopic retrograde pancreatography in detecting pancreatic carcinoma[12, 16] but arteriographic signs of pancreatic cancer may also overlap with those of pancreatitis.[17]

The failure to make a definite diagnosis of pancreatic cancer at surgery in the present case is not unprecedented. In a series of 26 cases of combined pancreatitis and pancreatic cancer at the Mayo Clinic, a correct operative diagnosis was made premortem in only 62% of the patients and even in the correctly diagnosed cases several operations were frequently required.[6]

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The Parotid and the Pancreas*

V. Effects of a Synthetic Prostaglandin Analog on Parotid Gland Secretion

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Effects of a synthetic prostaglandin analog—16,16-dimethyl prostaglandin E_2 methyl ester (16-diMe-PGE_2)—on parotid secretion were evaluated in eight dogs under anesthesia. Graded doses of 16-diMe-PGE_2 (0.3, 0.5, 1.0 and 2.5 μg./kg.) were administered intravenously with the parotid in the resting state or in response to urecholine (intravenous infusion or subcutaneous injections). Profound and prolonged inhibition of volume occurred. Amylase concentration was increased but output was unchanged. Bicarbonate concentration was increased but output was decreased. Nonsteroid inhibitors of endogenous prostaglandin synthesis did not alter these effects. Although these studies do not establish a physiologic role for prostaglandins in the regulation of salivary secretion, they do demonstrate a wide-ranging effect of prostaglandins on the gastrointestinal tract.

Prostaglandins are hydroxy-fatty acids derived from prostanoic acid. They are widely distributed in a variety of tissues and are biologically active in minute amounts. Numerous studies indicate that they may be concerned in some physiological and pathological processes affecting the gastrointestinal tract. They influence gastrointestinal motility,[1, 2] intestinal ion transport[3] and gastric[2, 4] and pancreatic secretion.[5, 6] Since several investigators have demonstrated a relationship between salivary and gastrointestinal secretions,[7-9] we studied the effects of a synthetic prostaglandin analog—16,16-dimethyl prostaglandin E_2, methyl ester (16-diMe-PGE_2)—on salivary secretion.

Methods

Parotid secretion was studied in eight adult mongrel dogs of both sexes weighing 10-16 kg. Each animal was deprived of food but not water for at least 18 hours prior to each experiment. Animals were studied no more than twice a week and never on con-

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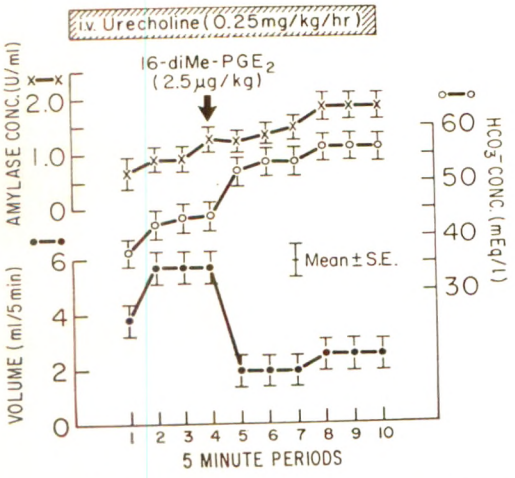


Fig. 1—Influence of 16-diMe-PGE_2 on parotid flow, bicarbonate and amylase concentration in response to urecholine 2.5 mg./kg./hr.

secutive days. A continuous intravenous infusion of 0.15 M sodium chloride was maintained throughout each experiment to allow for fluid losses and to permit intravenous injections. Parotid secretion was collected with the animals in the anesthetized state (Phenobarbital 0.35 mg./kg. I.V.). With the animal lying on its left side a Lashley saliva cup was placed over the papilla of the right parotid duct. The cup was maintained in position by gentle suction. Basal secretion was collected in five-minute periods for 30 minutes. Urecholine (Bethanechol chloride) was used as the stimulus for salivary secretion; it was administered by continuous intravenous infusion (0.25 mg./kg./hr.). These doses were found to elicit approximately 50% of the maximal secretory rate. After administration of the stimulant by either route, saliva was collected at five-minute intervals for at least 60 minutes.

Parotid secretion was studied in the following groups of experiments: 1. Single intravenous doses (0.05, 0.01, 0.3, 0.5 and 1.0 µg./kg.) of 16-diMe-PGE_2 in the resting gland. 2. Single intravenous doses (0.3, 0.5, 1.0 and 2.5 µg./kg.) of 16-diMe-PGE_2 with the parotid gland secreting in response to urecholine (0.25 mg./kg./hr.) infusion. 3. Single intravenous doses of 15-diMe-PGE_2 (2.5 µg.kg.) with the gland stimulated by urecholine 0.25 mg./kg./hr. subcutaneously. These responses were compared to those achieved by the administration of urecholine alone. 4. In separate experiments the animals were given oral indomethacin 5 mg./kg./day, in divided doses for 48 hours. Immediately prior to the experiment a further dose of 2.5 mg./kg. was given. The effects of intravenous 16-diMe-PGE_2 then were studied on the urecholine-stimulated gland.

The 16-diMe-PGE_2 and urecholine used in these studies were all from the same batches. No more than two doses a day were studied. The order of experiments and of doses was randomized. In the steady-state experiments, at least 30 minutes of collection was obtained to determine a plateau of secretion. The effects of 16-diMe-PGE_2 on parotid saliva were evaluated by comparison of the five-minute period of peak effect after 16-diMe-PGE_2 injection with the control five-minute response to urecholine alone.

In all experiments, saliva was collected under oil and the five-minute samples were analyzed individually for volume, bicarbonate concentration and output and amylase concentration and output. Bicarbonate, sodium and potassium were measured with a Technicon AutoAnalyzer and amylase by a modified Somogyi method.

Statistical significance was determined by the Student "t" test on the basis of paired observations between control values and values following prostaglandin administration.

Results

Basal secretion:—No stimulation of basal secretion occurred. Basal volume was

TABLE I

EFFECTS OF SINGLE INTRAVENOUS INJECTIONS OF 16-DI-ME-PGE_2 ON VOLUME, BICARBONATE AND AMYLASE CONCENTRATIONS, IN RESPONSE TO CONTINUOUS URECHOLINE INFUSION. RESPONSES IN THE INDOMETHACIN TREATED DOGS ARE ALSO SEEN

Urecholine 2.5 mg./kg./hr.	Volume ml./5 min.	Bicarbonate concentration mEq./l.	Amylase concentration U./ml.
Control	5.48 ± 0.15	43.7 ± 3.5	0.8 ± 0.16
16-diMe-PGE_2 2.5 μg./kg.	2.56 ± 0.03**	54.0 ± 2.6*	1.8 ± 0.01**
Indomethacin + 16-diMe-PGE_2 2.5 μg./kg.	3.70 ± 0.09**	48.1 ± 1.17*	1.4 ± 0.01*

* $P < 0.01$
** $P < 0.025$

decreased by 16-diMe-PGE_2 but, because salivary flow in the resting state in anesthetized dogs is very low, the changes were not very striking.

Stimulated secretion:—In the steady state experiments, a plateau of secretion was reached in 15 minutes in response to continuous urecholine infusion (Fig. 1). 16-diMe-PGE_2 injection resulted in a prompt reduction of volume, which lasted for at least 45 minutes. Volume was inhibited by 53% ($P < 0.02$) but amylase concentration and bicarbonate concentration (Table I) were both increased ($P < 0.01$). Amylase output was unchanged but bicarbonate output was reduced.

Single subcutaneous doses of urecholine stimulated parotid secretion within three to five minutes; peak secretory rate was reached in 10-15 minutes. 16-diMe-PGE_2 produced prompt inhibition of secretion. Inhibitory effects were dose related (Table II) and the threshold dose for inhibition of secretion was 0.3 μg./kg. Both bicarbonate and amylase concentrations were increased but whereas bicarbonate output was reduced, amylase output remained unchanged.

Cation composition was analyzed. Sodium concentration was slightly decreased, but this was not statistically significant ($P > 0.05$). The reduced concentration merely reflected reductions in volume. Potassium concentration was marginally increased at some doses but again this was not statistically significant ($P > 0.05$).

The nonsteroidal anti-inflammatory agent, indomethacin, did not prevent the inhibitory effect of 16-diMe-PGE_2 (Table I).

COMMENT

These results demonstrate that 16-diMe-PGE_2 is a potent inhibitor of parotid fluid and electrolyte secretion and that the inhibitory effect is dose related. The doses of 16-diME-PGE_2 found to inhibit parotid secretion are in the same range as those affecting gastric or pancreatic secretion.

Although amylase concentration was increased, there was no significant effect on amylase output. This is in sharp contrast to the effects of prostaglandins on the pancreas, where stimulation of enzyme output has been demonstrated.

Endogenous prostaglandin synthesis *in vitro* or *in vivo* is blocked by non-

TABLE II

EFFECTS OF GRADED DOSES OF 16-DIME-PGE_2 ON PAROTID SECRETION IN RESPONSE TO URECHOLINE BY SINGLE SUBCUTANEOUS INJECTION. THESE FIGURES REPRESENT THE PEAK FIVE-MINUTE VOLUME AFTER URECHOLINE INJECTION

Urecholine (2.5 mg./kg.) + 16-diMe-PGE_2 (μg./kg.)	Volume ml./5 min.	Bicarbonate concentration mEq./l.	Amylase concentration U./ml.
0	4.9 ± 0.45	40.0 ± 1.8	1.9 ± 0.2
0.3	3.9 ± 0.29*	46.8 ± 2.8	2.6 ± 1.0
0.5	4.1 ± 9.58*	48.9 ± 2.3*	2.8 ± 1.8*
1.0	2.9 ± 1.08**	50.9 ± 2.8*	2.9 ± 2.0*
2.5	2.8 ± 0.37**	51.1 ± 2.3	3.4 ± 1.7*

* $P < 0.01$
** $P < 0.025$

TABLE III

EFFECTS OF GRADED DOSES OF 16-DIME-PGE_2 ON CATION COMPOSITION OF PAROTID SECRETION

Urecholine (2.5 mg./kg.) 16-diMe+-PGE_2 (μg./kg.)	Sodium mEq./l.	Potassium mEq./l.
0	114.0 ± 3.3	5.9 ± 0.4
0.3	107.7 ± 5.4	6.7 ± 0.4
0.5	94.2 ± 4.3	6.2 ± 0.4
1.0	109.5 ± 1.8	7.1 ± 0.2
2.5	104.2 ± 8.6	6.0 ± 0.5

steroidal anti-inflammatory drugs,[10] probably by affecting prostaglandin synthesis.[11] Indomethacin did not alter the inhibitory effects of 16-diMe-PGE_2 in our experiments. This is not surprising as we used *exogenous* prostaglandin.

Prostaglandin F_2 has yielded different results. Hahn and Stadil[12] demonstrated that administration of PGF_2 to the anesthetized dog produced dose-related salivation. They found that salivation induced byPGF_2 was not the result of ganglionic stimulation but the PGF_2 produced salivation by an action of cholinoreceptors in the salivary gland.

Alterations in secretory cell ultrastructure have been noted in rat parotid glands[13] in response to the intravenous administration of prostaglandin E_1. A transient release of stored secretory materials from storage granules of the acinar cells was noted. Lillie[14] suggested that the observed ultrastructural changes in the parotid after prostaglandin E_1 treatment could be related to changes in levels or translocation of Ca^{++} displacement from a previously osmotically stable enzyme complex. He proposed that the action of prostaglandin E_1 on the parotid gland was due to a direct effect on intracellular Ca^{++} rather than adenyl cyclase or cyclic AMP which is a normal participatory event in parotid secretion.

Decreased visceral blood flow reduces glandular activity and its responsiveness to stimulation. This has been demonstrated for the stomach[14, 15] and the pancreas.[16] There is conflicting evidence whether the secretory inhibition is secondary to reduced blood flow or whether it is a primary effect on the secretory cells so that a reduction in blood flow is the result rather than the cause of the antisecretory effect.[17] It has

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been postulated that prostaglandins may act as local blood flow regulators.[18] The rapid degradation of most systemically administered prostaglandins in the lung[19] renders such a theory of local activity attractive.

The present study adds additional evidence that under experimental conditions prostaglandins markedly affect the function of the digestive tract. Although it is not yet clear whether they play a role in normal gastrointestinal physiology, there is evidence to suggest that they act as local regulators. Since prostaglandins can be synthesized and degraded in the same tissues, conceivably they could act (under physiological conditions) as local regulators rather than as circulating hormones. Indeed it has been suggested that prostaglandin synthesis and degradation probably occur within the same cell.

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Clinical Vignette

Asymptomatic Esophageal Perforation

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Rupture of the thoracic esophagus is usually accompanied by the dramatic clinical symptoms of severe chest, back or epigastric pain, dyspnea and dysphagia which may be associated with the findings of subcutaneous emphysema, mediastinal crepitance, temperature elevation, leucocytosis and circulatory collapse.[1-3] While an occasional case may have a more benign presentation, it is extremely rare to document a case of totally asymptomatic esophageal perforation. In this communication we report such a case, occurring from instrumentation, diagnosed incidental to a barium swallow and treated nonoperatively.

Case Report

A 62-year old white man presented with recurrent dysphagia. His past medical history revealed that he had undergone a partial thyroidectomy in 1946. In 1961 he developed intermittent dysphagia for solids and in 1971 had a myotomy for a stricture at the cricopharyngeal region with resolution of dysphagia. In January, 1977 he again complained of dysphagia for solids with food sticking in the xiphoid area. An upper gastrointestinal series at that time (Fig. 1) showed a hiatal hernia and a short stricture or ring. The patient underwent esophagoscopy in March, 1977 (Olympus GIF-D3) which disclosed a short concentric narrowing which was traversed with the endoscope. The biopsies of this area indicated normal squamous epithelium. Subsequently the patient was progressively dilated to size 54 French using Maloney dilators. No difficulty was encountered in dilatation. The patient did well but returned in July, 1977 because of recurrent dysphagia and was again dilated to 52 French with Maloney dilators. During dilatation there was no chest pain, discomfort or bleeding. The dilators were felt to pass easily without resistance and did not reveal blood upon withdrawal. Laboratory data revealed: Hgb. 15.2 gm.%; Hct., 43 vol.%; WBC, 7,300 cu. mm. with 60 polyps and 34 lymphs.

The patient did very well as an outpatient with no fever, chest pain or shortness of breath. His dysphagia was relieved and he was eating steak without difficulty. A routine barium swallow performed one week after the dilatation revealed a perforation near the cardioesophageal junction (Fig. 2). Although totally without symptoms, he was admitted for observation. Physical examination at this time revealed a pulse of 72 and regular, BP 140/80 mm. Hg. and a temperature of 36.5° There was no evidence of subcutaneous emphysema or mediastinitis on physical examination. A complete blood count included Hgb., 15.0 gm.%; Hct., 43 vol.% and WBC of 8,600/cu. mm. with a normal differential. Chest x-ray showed evidence of chronic obstructive pulmonary disease with no evidence of pneumomediastinum, pleural effusion or change from past films. During the period

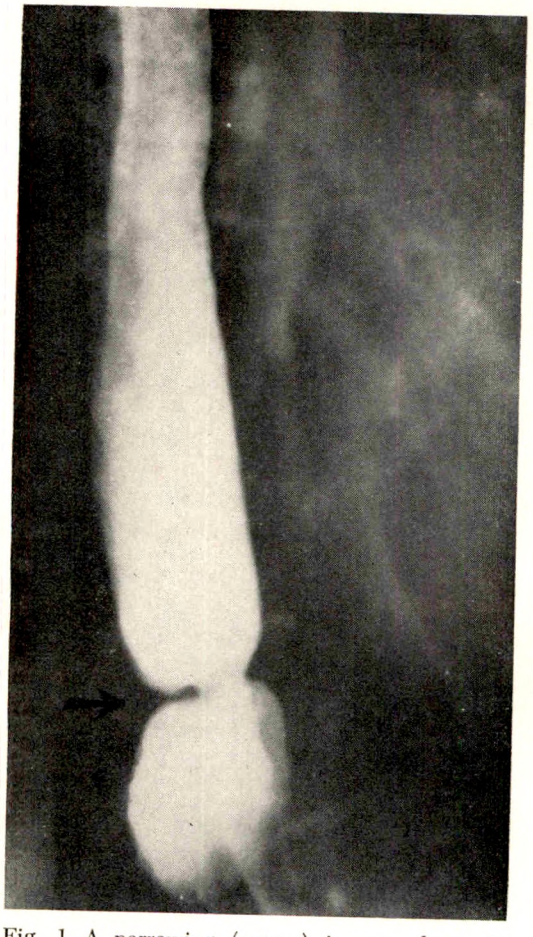


Fig. 1—A narrowing (arrow) is seen above the hiatal hernia at the cardioesophageal junction.

of hospital observation the patient remained asymptomatic, afebrile and did not have a leucocytosis. No specific therapy was instituted.

A follow-up barium study, done one week subsequent to radiological studies and two weeks after the dilatation, showed almost complete healing with only a trickle of barium at the site of the perforation (Fig. 3). The patient has continued to be asymptomatic and free of dysphagia.

Comment

Esophageal perforation is usually a catastrophic event. In a series of 71 patients

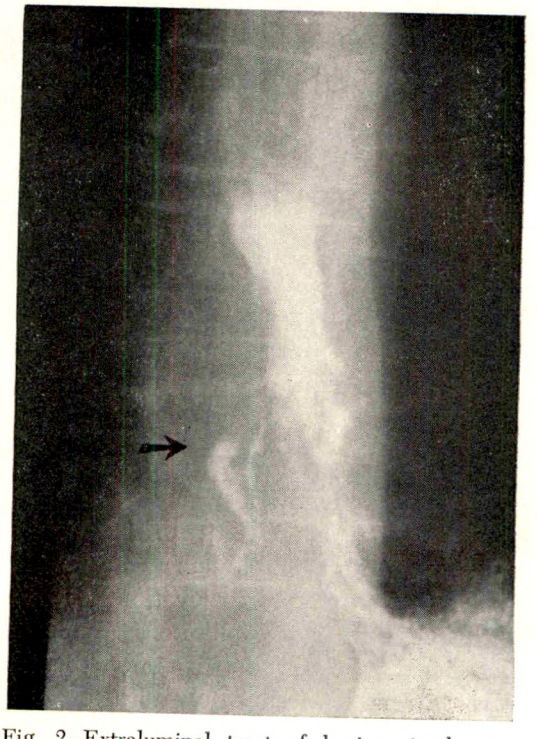


Fig. 2—Extraluminal tract of barium is demonstrated (arrow).

with spontaneous perforation not treated with surgical intervention the mortality was 100%.[4] With early operative treatment, entailing suture closure and drainage, the mortality has been reduced to a range of 20-30%.[3] Isolated cases of spontaneous perforation have been reported in which, because of very late clinical presentation or a benign course nonoperative approach has been pursued with success.[5-7]

Iatrogenic instrumental perforation of the esophagus is usually not as disastrous as spontaneous rupture. The usual causes of this include esophagoscopy, which is complicated by perforation in from 0.4-1.0%,[8] bouginage of strictures,[9] pneumatic dilatation for achalasia as well as from balloon tamponade with a Sengstaken tube.[10] The less complicated clinical course of iatrogenic perforation is explained by several factors including: 1) Earlier recognition in these frequently hospitalized patients. There is a

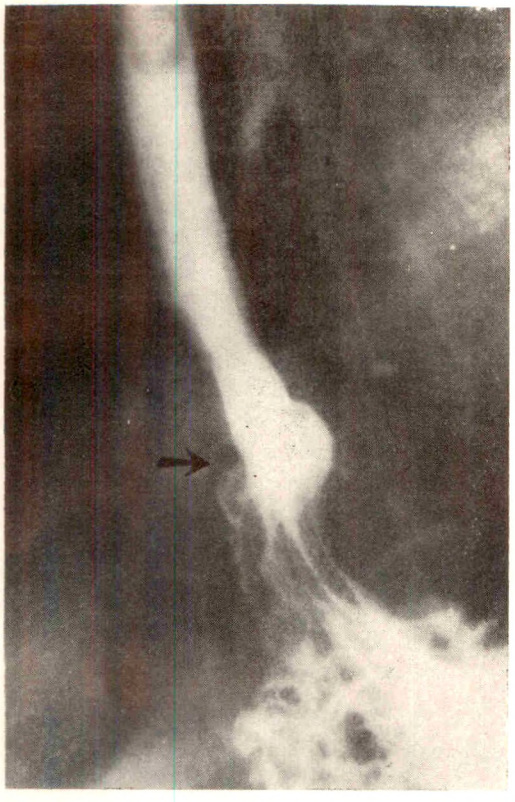


Fig. 3—Study one week later shows minimal trickle of extraluminal barium (arrow).

clear correlation of increased mortality with increased interval from perforation to initiation of therapy.[3] 2. Patients undergoing instrumentation are fasting, as opposed to the frequent excessive food and alcohol ingestion preceding emetogenic injury.[1] 3. Spontaneous esophageal rupture is forceful and extrusion pressure of the gastric contents into the mediastinum can result in chemical mediastinitis and/or pleuritis. Iatrogenic injury in contrast is often blunt and less forceful, giving a greater chance for confinement to the mediastinal space and avoiding respiratory embarrassment.

A nonoperative approach to instrumental perforation consisting of high dose antibiotics, nasogastric suction and bed rest has been advocated.[11, 12] Mengoli and Klassen nonoperatively treated 18 patients with endoscopically induced perforation and reported a mortality of only 6%.[11] The major hazard of this approach is that observation following the initial perforation may result in delay of surgery until mediastinitis and other complications have ensued.[13]

In our patient the diagnosis of esophageal perforation into the mediatinum was made seven days postinstrumentation by a routine barium swallow. The patient was not only asymptomatic with no further dysphagia but felt improved because of increased dietary tolerance. He was then observed in the hospital and did not require antibiotics, prolonged fasting or surgery. This patient exemplifies that patients may undergo small tears during instrumentation of the esophagus but remain, as our patient, totally without clinical symptoms. The question arises if these patients are then discovered incidentally because of barium swallow or chest x-ray must they then undergo surgical correction or vigorous antibiotic treatment with drainage? This question will require a prospective study. We feel, however, that in a patient with truly asymptomatic esophageal perforation application of this therapeutic approach seems most rational.

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Clinical Vignette

Carcinoma of the Cervix After Treatment with Prednisone and Azathioprine for Chronic Active Hepatitis

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A 24-year old woman with chronic active hepatitis developed carcinoma of the cervix, *in situ*, after receiving 1,000 gm. of azathioprine and 250 gm. of prednisone during a period of 5½ years. This occurrence emphasizes one of the risks of immunosuppressive therapy and we recommend careful surveillance for cancer in patients so treated. The evidence that hepatitis may be associated with an increased incidence of cancer of the cervix is reviewed.

Chronic active hepatitis is a serious disease which may arise in young patients. Current therapy requires potent drugs which may be administered for long periods of time. The physician must balance the risk of his treatment against the risk of the patient's disease. Without treatment, the prognosis in chronic active hepatitis is so dismal that long-term therapy with a corticosteroid, with or without azathioprine, is advised.[1] Malignancy, however, may be a grave risk associated with chronic immunosuppressive therapy.

Case Report

Our patient, a white woman, developed jaundice and malaise at age 19. Her serum contained hepatitis-associated antigen. Initially, she improved but seven months later a relapse occurred manifested by malaise, pruritus and jaundice. A percutaneous liver biopsy demonstrated chronic active hepatitis. Treatment with 50 mg. azathioprine and 30 mg. prednisone daily was effective in returning the tests of liver function to normal. Symptoms disappeared, so the dosage of prednisone was slowly reduced. Yearly liver biopsies showed inflammation of the liver so therapy was continued. After four years of therapy the routine Papanicolaou smear was interpreted as Class II (probably normal/slight atypia), so this examination was performed every six months instead of every 12. Another report of Class II was received but thereafter the "Pap" smears were reported as normal.

After five and a half years of treatment and when the patient was 24 years old, the cytologic diagnosis from a "Pap" smear was severe dysplasia. By this time, the patient had taken 1,000 gm. of azathioprine and 250 gm. of prednisone. A vaginal hysterectomy was performed for carcinoma *in situ* of the cervix. Since that time, the patient has taken prednisone without azathioprine. She remains well, and liver function is normal.

Comment

There are three possible interpretations of the occurrence of carcinoma of the cervix in this patient with chronic active hepatitis treated with immunosuppressive drugs. We

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can only speculate which possibility occurred in this young woman.

First, the cancer may have arisen independently of her liver disease and its therapy.

Secondly, the cancer may have been caused by chronic liver disease. Untreated hepatitis has been associated with an increased incidence of atypia of the cells of the cervix.[2] Another study of 36 women with hepatitis revealed that 12 (33%) had positive "Pap" smears and one had a negative "Pap" smear but had carcinoma *in situ* at autopsy.[3] Only two had received corticosteroids. Nine of the 12 with positive smears had biopsy of the cervix and six had intraepithelial carcinoma. One thousand consecutive patients without hepatitis from the same institution served as a control population; positive cytology was found in 4%. Most of the patients in these two reports suffered from acute viral hepatitis; the number with chronic active hepatitis is not given.

Two women with chronic active hepatitis have developed ovarian cystadenocarcinoma and one woman a histiocytic lymphocytic lymphoma. These three women had received prednisone for four to six years but none had received azathioprine.[4]

Thirdly, immunosuppressive therapy may have caused the malignancy. This topic has been reviewed in depth with the conclusion that there is such an association, particularly in patients in whom an organ has been transplanted.[5] Azathioprine alone has been followed by carcinoma of the bladder in two patients[6] and another developed plasmacytoma of the cervix.[7] A young woman who received azathioprine for two weeks for a renal allograft was discovered to have severe cervical and vaginal dysplasia.[8]

A patient similar to ours was reported by Schramm.[9] A 32-year old woman with chronic active hepatitis was treated with azathioprine for 15 months and developed "severe cervical dysplasia." The patient was not given steroids.

It behooves physicians who are administering immunosuppressive agents to watch their patients very carefully for the development of cancer and to investigate promptly any new symptoms. More data is needed to confirm the reports of increased malignancy of the cervix in women with hepatitis. If this is true, women with hepatitis who are treated with immunosuppressive agents may prove to be at even greater risk for carcinoma of the cervix.

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Clinical Vignette

Concomitant Alcohol and Drug Abuse Enhancing Acetaminophen Toxicity

Report of a Case

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Acetaminophen, a commonly prescribed analgesic in the United States, is noted for its safety in therapeutic doses. There are nearly 200 preparations on the market containing acetaminophen.[1] Moreover, it is prescribed preferably to aspirin for patients such as alcoholics who are susceptible to acute mucosal gastrointestinal lesions. The British literature has reported numerous cases of acetaminophen overdose with severe hepatic and renal injury, yet the first case report published in this country was in 1971.[2] Not until recently has attention been focused on the consequences and incidence of acetaminophen hepatotoxicity.[3-5]

With therapeutic doses, in the range of 600-1,800 mg., there is a wide margin of safety. Mild liver injury is generally detectable after ingestion of more than 10 gm. and severe liver injury is usually reported only after 15-20 gm., acetaminophen overdosage.[6] Ingestion of substances, however, which induce microsomal enzymes, such as ethanol, phenobarbitol or meprobamate[7] may be expected to enhance acetaminophen-induced hepatotoxicity or lower the dose at which severe damage occurs. This report substantiates this view and suggests that those individuals habitually using hepatic enzyme inducers, many of which are commonly prescribed in clinical practice, have a reduced margin of safety for acetaminophen-induced hepatic injury.

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Case Report

K. M., a 36-year old Caucasian female, was transferred to the Westchester County Medical Center from a local hospital because of hepatic and renal failure noted two days after taking at least 30 Tylenol® tablets (9.75 gm.) for headaches. The patient ingested alcohol daily for several years and was drinking heavily on the day of the Tylenol ingestion. She denied any previous liver problems. The patient was taking oral contraceptives and Meprobamate for several years.

On physical examination, the patient was found to be obtunded with marked jaundice and spider nevi on the upper arms and shoulders There was no hepatosplenomegaly but asterixis was noted.

Laboratory investigations showed a hemoglobin of 12.9 gm.% and the white blood count was 14,000/cu. mm. Plasma

TABLE I

LABORATORY DATA

Date	SGOT (10-50 mU./ml.)	SGPT (5-40 mU./ml.)	Bili. I/D (up to 1.0 mg./dl.)	BUN (up to 20 mg./dl.)	Creat. (0.8-1.2 mg./dl.)	Pro-time (T/C sec.)
9/24	1960		18.6/13.8	90	12	28.9/12.0
9/25	490		10	58		41.2/11.7
9/28	184	303	30	31	5.1	20.2/12.7
10/1	410		29.7/25	90	14.5	16.8/12.4
10/4	211		26.8/	94	8.4	
10/7	209		27.3/26	35	4.7	15.8/11.9
10/11	340	293	32.4		8.6	13.8/10.5
10/14	410	86	30	71	5.4	
10/18	290		29.2		2.6	

acetaminophen level done here after the transfer was zero. The urine contained a large amount of blood and granular casts. The rest of the laboratory values are shown in Table I.

Initially, the patient was treated with peritoneal dialysis, I.V. fluids, Vitamin K and lactulose. On the second hospital day, a pericardial friction rub was heard but serial electrocardiographs and CPK isoenzymes were within normal limits. Peritoneal dialysis was discontinued on the fourth hospital day. Subsequently, the patient developed paralytic ileus which resolved with nasogastric suctioning. On the eighth hospital day the patient became hypotensive with a deteriorating mental status and a bleeding diathesis was noted. The hemoglobin was 8.8 gm.% with 96,000 platelets. She was transfused blood and fresh frozen plasma. Dopamine was needed to maintain the blood pressure. Despite therapy, the patient became comatose and peritoneal dialysis was restarted. Subsequently, there was improvement in her mental status and resolution of the bleeding disorder. Renal functions gradually returned to normal but her liver functions showed persistent abnormalities with marked hyperbilirubinemia. Tests for Hepatitis B antigen were repeatedly negative.

Comment

This patient was admitted to a local hospital with a diagnosis of viral hepatitis and, because of a low index of suspicion, did not receive specific therapy for acetaminophen overdose. An acetaminophen level was obtained several days later, a time when it can add little diagnostic or prognostic information, since the drug is rapidly absorbed and metabolized.[3] Also a single determination has not proved to accurately predict the degree of liver necrosis.[8]

This patient took about 30 Tylenol tablets (9.75 gm.), a dose which is not usually associated with severe hepatotoxicity.[6] Despite this, she developed all the clinical and biochemical characteristics of extensive hepatic and renal injury usually seen after a massive overdose. In fact, a bilirubin elevation of greater than 4 mg./100 ml. and a prothrombin time ratio of 2.2 or greater as was seen in this case, correlates with severe liver injury, encephalopathy and increased mortality.[8] Unfortunately, liver biopsy had to be postponed because of persistent ascites and coagulation abnormalities. Therefore, the extent of liver cell injury could not be corroborated histologically. But when liver biopsy was done several months later, the tissue was fragmented and the histological pattern was consistent with early cirrhosis.

Perhaps the history of ethanol and Meprobamate ingestion and the use of oral contraceptives and antihistamines, may explain the extensive hepatic tissue damage suffered by this patient despite a relatively small acetaminophen overdosage. Many previous reports have presented cases in which acetaminophen overdosage was accompanied by the ingestion of ethanol and various drugs, notably barbiturates.[2, 9]

Scott and Stewart note that this association is present in the majority of their cases.[10] Moreover, those patients with multiple drug ingestion or ethanol abuse seem to develop particularly severe liver injury.[7] In fact, it has been suggested that there is less time available for effective treatment in the patient with an alcohol damaged liver.[10] One study correlated the extent of hepatic injury with a history of alcohol or drug ingestion in patients with acetaminophen overdosage. They showed that the hepatic necrosis is potentiated by the use of alcohol and barbiturates.[11] The way these substances promote hepatic injury is con-

sistent with the mechanism of acetaminophen toxicity elucidated by Mitchell and his co-workers.[12]

Hepatic microsomal enzymes, the cytochrome P-450 mixed function oxidase, form a toxic intermediate of acetaminophen which binds covalently with hepatocyte macromolecules causing cell necrosis. Normally, glutathione, binding preferentially with a toxic matabolite, forms a nontoxic product mercapturic acid which is excreted in the urine. This accounts for the great safety of acetaminophen in therapeutic doses. When glutathione stores are overwhelmed because of depletion by massive acetaminophen doses, or when formation and binding of the toxic metabolite is enhanced, hepatocellular necrosis ensues.

Experimentally, pretreatment with hepatic enzyme inducers such as phenobarbital, increases the rate of acetaminophen metabolism suggesting that liver injury after human overdosage may be intensified in patients with such compounds.[13] Lieber has shown that chronic administration of ethanol to rats and man results in the increased activity of a variety of microsomal, drug-detoxifying enzymes[14] and Conney, in an extensive review of microsomal enzyme induction, listed numerous drugs capable of this activity that are commonly prescribed in clinical practice.[7] As noted, our patient ingested several of these compounds and developed extensive liver necrosis with a relatively small acetaminophen overdosage.

Our experience with this patient prompts us to question the common notion that acetaminophen is safer than aspirin in alcoholics. The physician must recognize that there is a decreased margin of safety for acetaminophen hepatotoxicity, not only in the setting of chronic ethanol ingestion but also with the habitual use of other enzyme-inducing substances. It should be considered whenever acetaminophen is prescribed or an overdosage is suspected that such patients are at high risk to develop severe necrosis despite a relatively small dose.

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Clinical Vignette

Hereditary Hemorrhagic Telangiectasia in Three Black Men

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Hereditary Hemorrhagic Telangiectasia (HHT) has been reported to be rare in blacks. We recently have seen three black men with this disease, two of whom had gastrointestinal bleeding. HHT may not be as rare in blacks as previously reported.

Introduction

Hereditary hemorrhagic telangiectasia (HHT) is a familial disease characterized by mucosal surfaces containing telangiectases which are thin-walled and fragile. Since the vessels have poor support and are poorly contractile, profuse bleeding may occur after minor trauma.[1] It has been reported to be unusual in blacks. In a period of one year, however, three black patients with this disease were seen in a Veterans Administration Hospital and a University Hospital serving a predominantly black population (Table I).

Case Reports

Case 1:—B. B., a 42-year old black man with a history of excessive use of alcohol, was admitted in August, 1975 for hematemesis. He had four prior admissions for gastrointestinal bleeding dating to 1971 and had been diagnosed as ulcer disease and variceal bleeding in the past by endoscopy and x-ray studies.

On the morning of admission he was awakened by nausea and vomited blood. Past history included hypertension and diabetes. Current medications were methyldopa, insulin, antacids, $FeSO_4$. He denied recent alcohol or aspirin use. Family history was unremarkable.

Physical examination revealed a blood pressure of 180/110 and a pulse rate of 120 without orthostatic changes. Examination otherwise was unremarkable.

Emergency endoscopy revealed probable bleeding at the gastroesophageal junction but the examination was felt to be unsatisfactory because of large clots in the stomach. There were no varices. Selective arteriography revealed focal bleeding from the left gastric artery near the gastroesophageal junction and vasopressin was infused intra-arterially with control of the bleeding. After the patient was stabilized and transfused, he was noted to have multiple, small, punctate red lesions on his lips. Repeat endoscopy revealed similar 1-2 mm. punctate spots in the antrum, consistent with HHT (Fig. 1). He did well and was discharged on antacids, $FeSO_4$, methyldopa and insulin. He has done well with no recurrent massive bleeding since.

Case 2:—J. H., a 62-year old black man, with a history of alcoholism was admitted in March, 1976 for lightheadedness for two days. He had a history of eight

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TABLE I

Patient	Age	Sex	Race	Family history	Epistaxis	Admission for gastrointestinal bleeding	Previous diagnoses	Location of lesions by endoscopy
B. B.	42	Male	Black	Negative	No	4	Ulcer varices	Antrum
J. H.	62	Male	Black	See Fig. 2	No	8 before, 3 since	Ulcers gastritis	Duodenum
C. V.	38	Male	Black	Cousin son	No	None	Epistaxis	Not done

prior admissions for gastrointestinal bleeding dating to 1969 and had been diagnosed as ulcer disease and gastritis by endoscopy. Recent use of alcohol or aspirin was denied. Also denied at this time was a family history of bleeding.

Physical examination revealed a blood pressure of 90/60 without postural change. On standing however, his pulse rose from 100 to 120. A nasogastric tube was passed and red blood was returned. Endoscopy revealed no active bleeding site but did show a large clot covering the greater curvature.

Blood transfusion of two units was effected and the vital signs rapidly stabilized. Re-examination revealed two 2 mm. red telangiectases on the lower lip. Additional blood transfusions were given until the hematocrit reached 35%. Repeat endoscopy was then done. This revealed four telangiectases in the duodenum, measuring 2 mm. each, that bled easily when touched.

Clinical improvement followed and the patient was discharged on $FeSO_4$ and antacids. He has subsequently been admitted three more times for anemia, orthostatic hypotension and guiac positive stools. Work-up by x-ray revealed no new sources of bleeding. His family history was reviewed and he was found to have a Caucasian ancestor (Fig. 2).

Case 3:—C. V., a 38-year old black man, was admitted because of shortness of breath and abdominal pain. He first came to the University Hospital in April, 1976 for a nosebleed. There was a history of frequent epistaxis since childhood. Melena occurred only following a nosebleed. He was diagnosed as having HHT and a submucous resection of the nose was done for septal deviation and recurrent epistaxis. A cousin and one of his two sons were found to have recurring nosebleeds but no other family member had this problem and in none was there gastrointestinal bleeding.

Physical revealed a blood pressure of 140/75, pulse of 124 (supine); blood pressure 95/70, pulse 147 (sitting). Temperature was 41° C. Two telangiectases were noted on the lips. Lung examination disclosed mild wheezing and rhonchi. Stools were guiac negative. Nasogastric aspirate was initially negative for blood but nasal bleeding occurred when the tube was passed.

Laboratory tests revealed an Hct. of 33%; Hgb. of 10.3; WBC of 7,700; normal red cell indices; serum iron, 21; total iron binding capacity, 252; serum amylase, 155; SGOT, 163; SGPT, 8; serum alkaline phosphatase, 94; serum bilirubin, 2.5 (total). Blood cultures were negative.

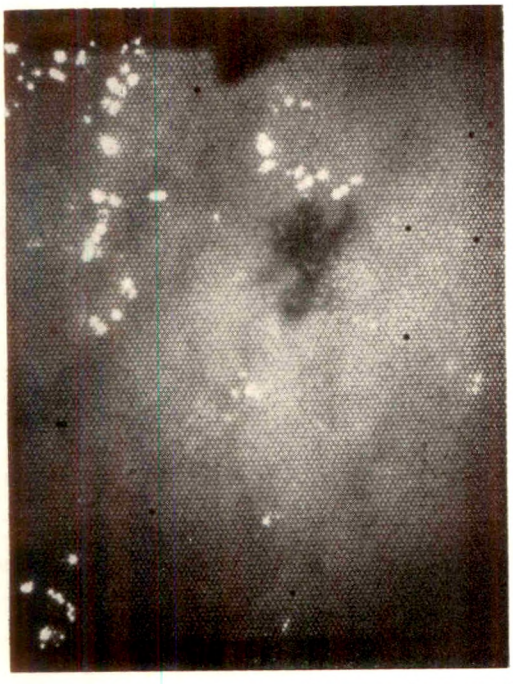


Fig. 1—Telangiectases seen during endoscopy of Case 1.

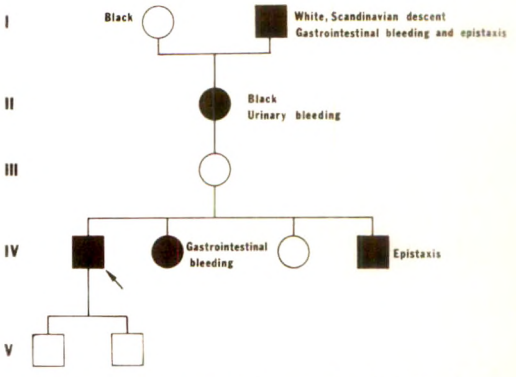


Fig. 2—Genetic background of Case 2.

On the second hospital day a cellulitis of the right arm appeared and a smear of an aspirate revealed *Staphylococcus aureus*. This responded to methicillin. Stools were intermittently positive for blood and the hematocrit slowly fell to 28%. The latter was felt to be secondary to recurrent epistaxis, rather than to gastrointestinal bleeding. Endoscopy was refused.

Comment

HHT is inherited as an autosomal dominant with a high degree of penetrance. Skipped generations may be explained by affected individuals who never have obvious bleeding. It is reported to occur most commonly in Anglo-Saxon, Latin, Scandinavian and Jewish persons[1] and also has been reported in a Chinese family[2] Up to now it has been reported in only 14 blacks and of these, nine were in one family and three were in another. Four of the 14 black patients had gastrointestinal bleeding.[3-7] This is consistent with a previously reported series of 159 patients in whom 81% had epistaxis and 13% were found to have gastrointestinal bleeding.[8]

Cutaneous, oral, or nasal telangiectases are seen in 96% of the patients with this disease.[8] Patients have been reported, however, with gastrointestinal bleeding and no external lesions.[9, 10] In our two patients with intestinal bleeding, mucosal lesions were not identified initially on many admissions and were seen only after hematocrit was raised above 30% by transfusion. Likewise, endoscopy done while actively bleeding, or shortly thereafter, failed to reveal the lesions. They were seen, however, when the patients were stable. Perhaps the lowered arterial pressure from severe bleeding leads to collapse of these poorly supported vascular structures, thus making identification difficult early in the course.

The rarity of reports of HHT in blacks may be due to poor recognition of the lesions in dark-skinned people.[2] The lesions are obscured by increased skin pigmentation and may easily be overlooked if not carefully sought. Indeed, it is possible that the disease is not any more unusual in blacks but has not been recognized because of failure to find the lesions. In keeping with this is the fact that we have identi-

fied three unrelated black patients with HHT within one year. It is also possible that HHT really is rare in blacks unless there is a Caucasian in the family tree as was true of one of our patients. In any event, HHT should be considered in patients with unexplained, chronic, or repeated acute gastrointestinal bleeding whatever the race of the patient.

Since bleeding is from a localized point, the bleeding vessel may be amenable to treatment by endoscopic laser coagulation[11] or endoscopic electrocautery.[12]

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Clinical Vignette

Endoscopic Retrograde Cholangiopancreatography Diagnosis of Choledochal Cyst

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A 55-year old woman with a choledochal cyst (congenital cystic dilatation of the common bile duct) is described. The cyst was diagnosed by endoscopic retrograde cholangiopancreatogram (ERCP). The clinical, radiographic and surgical features of this disorder are reviewed.

Introduction

Choledochal cyst (congenital cystic dilatation of the common bile duct) is a very rare condition in adults. These cysts are commonly distinctive in children under the age of ten. Even in this age group they are considered rare. The classical triad of a choledochal cyst includes pain, jaundice and a palpable right upper quadrant mass. This triad was found in only 63% of the 232 cases reported by Tsardakas and Robnett[1] and in only 21% of the 94 cases analyzed by Alonso-Lej, et al.[2] Diagnosis of choledochal cyst usually is made during laparotomy. In nonjaundiced patients, oral cholecystogram and/or intravenous cholangiogram may yield the diagnosis. In jaundiced patients where the diagnosis may be more difficult to make, one may consider doing ERCP and/or percutaneous transhepatic cholangiogram. This paper reports a case of choledochal cyst diagnosed by ERCP.

Case Report

L. G., a 64-year old Caucasian female, was referred to Allegheny General Hospital in March, 1973 with a diagnosis of cirrhosis and possible pancreatic carcinoma. This diagnosis was based on a history of "silent" jaundice of six months' duration, anorexia, weight loss and pedal edema. An open biopsy of the liver was reported to show cirrhosis with bile stasis. Detailed questioning revealed that the patient had experienced gallbladder symptoms 25 years previously. These symptoms abated when she followed a low fat diet. One year prior to admission, an oral cholecystogram failed to visualize the gallbladder. Surgery was recommended but the patient refused because she felt too sick.

Examination revealed jaundice, ascites, hepatomegaly with a prominent left lobe of the liver and pedal edema. There were no other abdominal scar masses or splenomegaly. Laboratory studies revealed; WBC, 7,200; HCT., 36.7; total bilirubin, 12 mg.%; direct bilirubin, 8.6 mg.%; total protein, 7.8 gm.; albumin, 2.0 gm., globulin, 5.8; alkaline phosphatase, 16.5 Bessie-Lowry units (normal 1.1-2.5).

An upper gastrointestinal series on 12 March 1973 showed an area of irregularity in the antrum which was considered to be neoplastic.

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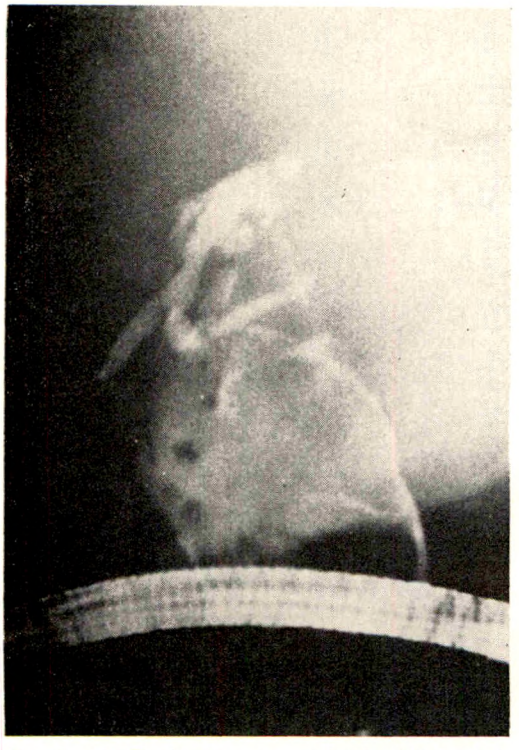


Fig. 1—ERCP showing incompletely filled choledochal cyst with intrahepatic bile ducts.

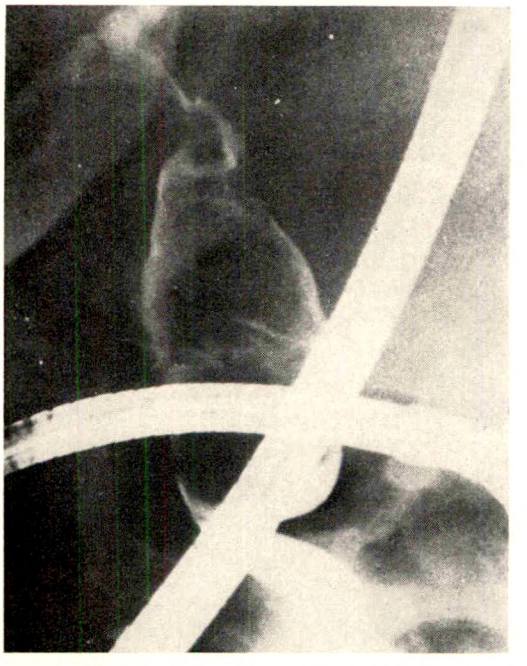


Fig. 2—Choledochal cyst with contrast material outlining the walls. Note the normal calibered proximal and distal portion of the common bile duct.

Gastroduodenoscopy and ERCP on 15 March showed multiple large ulcerations of the antrum and a choledochal cyst. (Figs. 1 and 2) The gallbladder was not visualized.

Laparotomy on 19 March showed a fist-sized (10 × 8 cm.) choledochal cyst. The cyst contained multiple stones and bile-stained mucinous debris. The gallbladder and cystic duct were absent. A choledochocystojejunostomy was performed and a T-tube was placed in the cyst. A T-tube cholangiogram subsequently showed the persistent cystic lesion (Fig. 3).

Review of the liver biopsy showed changes consistent with biliary cirrhosis. The patient was discharged with persistent jaundice. The T-tube was left in place. The patient died two months later at another hospital.

Comment

The clinical features of choledochal cyst include pain, jaundice and right upper quadrant mass. This triad was seen in 21% of 94 cases reported by Alonso-Lej, et al[2] and 63% of 232 cases analyzed by Tsardakas.[1] In Lee et al's series of 97 cases,[3] the triad was seen in only 19.6% of the cases. When individually studied, jaundice occurred in 73.4% of the cases, pain in 64.89% and mass in 59.57% of the cases studied by Alonso-Lej, et al. In Lee, et al's series, 3.1% of the cases did not have any features of this triad.

Choledochal cyst is thought to be extremely rare in adults. Lee, et al, while reviewing the literature on 88 cases of choledochal cyst together with nine of their own, described the incidence to be 16% between 21-40 years of age and only 8.4% over 41 years of age. Our patient and four others

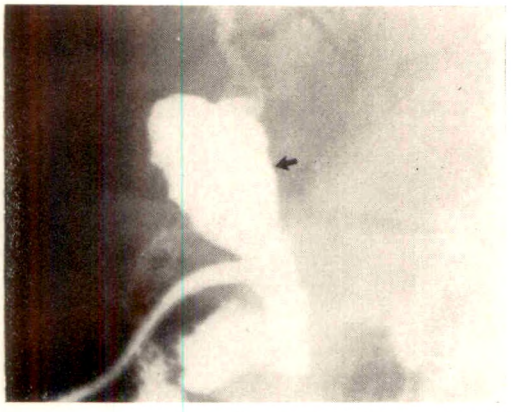


Fig. 3—T-tube cholangiogram showing completely filled choledochal cyst (arrow) and a normal appearing distal and proximal common bile duct. Contrast material is also seen in the duodenum.

studied by us, were all over 55 years of age. We suggest that age should not be a factor when you consider the possibility of choledochal cyst. Why one patient develops symptoms at an early age and the other at a late age (considering it's etiology to be congenital in origin) is not clear. In fact, Shocket, et al[4] discovered a choledochal cyst in an unborn fetus and Madding[5] described a patient with a cyst in as late as the eighth decade of his life.

The complications of choledochal cyst are largely due to biliary obstruction. These complications include stone formation, suppurative cholangitis, biliary cirrhosis, hepatic abscess and thrombosis of the portal vein.[2]

An increased awareness of choledochal cyst and the availability of more advanced radiological methods have made it possible for the preoperative diagnosis of choledochal cyst from the approximately 13% reported in 1943,[6] to 67% in the review of 1969.[3]

Various diagnostic methods have been used in the diagnosis of choledochal cyst. Jesseman and Treasure[7] emphasized the use of roentgenograms. In plain x-ray films, a mass may be visible in the right upper quadrant with displacement of the gas shadows of the stomach and colon. An upper gastrointestinal series may reveal an anterior, inferior and medial displacement of the duodenum or gastric antrum as seen in our patient. Oral cholecystograms are not of much use, especially when patients are jaundiced.[7]

Intravenous cholangiograms are of greater value and are frequently positive. Accuracy of diagnosis by I.V.C. is inversely proportional to the degree of jaundice present. This procedure may be improved by using tomography.[8]

The preoperative diagnosis of choledochal cyst in a patient with jaundice presents a problem. Recently Tada, et al[9] and Williams, et al[10] reported the use of isotopic scanning as an effective method of demonstrating cystic lesions. Ultrasonic technics have been successfully used by Russell, et al[11] in the diagnosis of cyst. The use of transjugular cholangiography[12] has not yet become popular. Percutaneous transhepatic cholangiography seems to be very helpful in diagnosing jaundiced patients.[12-14] It is being used more and more in recent years but this method is not without complications.

With the advent of ERCP, visualization of the biliary tree has become a simple procedure when performed by expert endoscopists. With this procedure, both the intrahepatic and extrahepatic duct systems and the pancreatic duct system can be visualized. This provides a useful basis for surgical management. The salient features of ERCP diagnosis of axial choledochal cyst are: 1. Cystic dilatation of the common bile duct with no signs of distal obstruction. 2. Relatively normal diameter duct proximal and distal to the cyst. 3. The cyst may contain stones, debris and other things that may be visualized.

To our knowledge, the only other case report of choledochal cyst (intrahepatic) diagnosed by ERCP has been Thomas, et al.[15]

The surgical treatment of the cyst is dependent on the location and extent of the lesion as determined by intraoperative cholangiogram. The procedure of choice in axial choledochal cyst is choledocystojejunostomy.[1] Choledochocele, a variant of choledochal cyst, is treated by marsupialization of the cyst into the duodenum by removal of the common wall.

Our patient presented with "silent" jaundice of approximately six months' duration and unfortunately already had biliary cirrhosis at the time of the diagnosis. The gallbladder and cystic duct were congenitally absent. A choledochocystojejunostomy was performed and a T-tube left in place at the time of discharge.

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Clinical Vignette

Hepatocellular Carcinoma in a Hepatitis B Surface Antigen Carrier and Treatment with Adriamycin

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A case of hepatocellular carcinoma (HCC) occurring in a 32-year old Caucasian male carrier of hepatitis B surface antigen (HBsAg) is reported. This case further supports the hypothesis that hepatitis B infection may be involved in the causation of HCC. Treatment of the HCC with Adriamycin was carried out in this case with little success. The association between hepatitis B and HCC is discussed.

Case Report

The patient was a 32-year old male who was first admitted to Royal Perth Hospital in January, 1976 with burns from hydrofluoric acid. He recovered and was discharged in February, 1976. In August, 1974 he was found to be positive for hepatitis B surface antigen and he then remained positive. In July, 1976 he was readmitted for investigation of right hypochondrial pain, anorexia and severe weight loss (9 kg.). Physical examination revealed that he was not jaundiced, anemic or cyanosed. His heart was relatively normal and the blood pressure was 140/80 mm. Hg. His lungs were clinically clear. Palpation of his abdomen revealed that his liver was markedly enlarged to about 10 cm. below the right costal margin and affecting, predominantly, the right lobe. The liver surface was firm and smooth and not tender. The spleen was only just palpable. There was no evidence of lymphadenopathy and no other physical findings of significance. Investigations showed the following: Hgb. was 171 gm./l.; WBC was 7.3 × 10^9/l. with a differential count of 63% neutrophils, 27% lymphocytes, 9% monocytes and 1% eosinophils. The sedimentation rate was 16 mm./hr. The prothrombin time was 13 seconds compared to a control of 10 seconds. Serum calcium, phosphate, uric acid, creatinine kinase and lactic dehydrogenase were all normal. Liver tests are shown in Table I. Hepatitis B surface antigen (HBsAg) was found to be positive but the hepatitis B surface antibody was negative in the blood. A clinical diagnosis of hepatomegaly with hepatitis B surface antigenemia was made. Malignancy of the liver was clinically suspected. A liver scan showed a space defect in the right lobe of the liver indicating the possibility of a hepatocellular carcinoma (Fig. 1). The alpha-feto-protein was also positive giving

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TABLE I

LIVER TESTS BEFORE AND DURING ADRIAMYCIN THERAPY

Date	Adriamycin (I.V. dose)	Liver Tests			
		Bil. (μmol/l.)	SAP (U./l.)	Alb. (gm./l.)	SGOT (U./l.)
1/29/76*	–	14	196	26	69
7/22/76	–	11	630	41	55
8/23/76	–	7	932	32	48
8/25/76	10 mg.	–	–	–	–
8/26/76	–	13	1,370	33	79
8/30/76	–	6	1,670	30	111
9/1/76	50 mg.	–	–	–	–
9/3/76	–	8	1,550	33	86
9/7/76	–	5	1,350	32	65
9/14/76	–	6	949	36	55
9/21/76	60 mg.	8	821	32	58
9/24/76	–	11	791	33	49
9/27/76	–	6	741	33	38
10/18/76	–	9	2,040	31	111
10/20/76	60 mg.	8	2,310	30	98
10/25/76	–	16	1,960	32	41
12/6/76	–	39	3,210	32	129
12/8/76	60 mg.	33	3,410	30	108

* Liver tests on admission for hydrofluoric acid burns. The liver was not enlarged clinically.
Bil = serum bilirubin (normal < 20).
SAP = serum alkaline phosphatase (normal < 300).
Alb = serum albumin (normal 35-45).
SGOT = serum glutamic oxaloacetic transaminase (normal < 42).

strong support to the diagnosis of a primary hepatocellular carcinoma. Hepatic angiography was done and this showed a diffusely abnormal liver with areas of hypovascularity. There was evidence of arterial and venous invasion by infiltrative tissue. The appearances were those seen typically with diffuse hepatocellular carcinoma. A liver biopsy confirmed the presence of hepatocellular carcinoma.

The patient was given a course of Adriamycin. After a test dose of 10 mg. intravenously, 50 mg. was administered by intravenous drip, making a total first dose of 60 mg. A further three doses of 60 mg. each were given at intervals of about three to six weeks. The effect of Adriamycin on serial liver tests is shown in Table I. Hemoglobin, white cell count, platelet count, blood urea, creatinine and serum electrolytes all remained within normal limits during the course of Adriamycin. HBsAg and alpha-feto-protein remained positive throughout the course of his illness. Serial

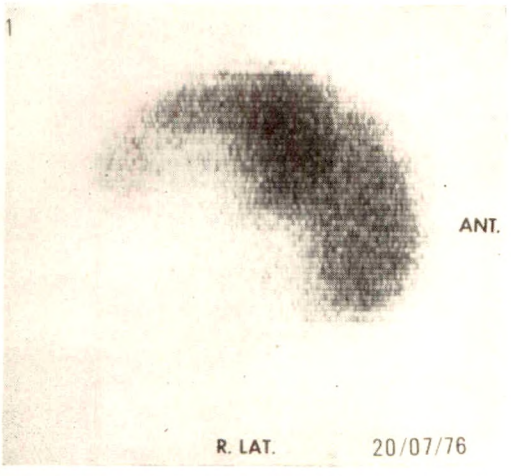


Fig. 1—Liver scan (right lateral view) done before Adriamycin treatment showing large filling defect in the right lobe of the liver. Hepatocellular carcinoma was confirmed by positive alphafoetoprotein and liver biopsy.

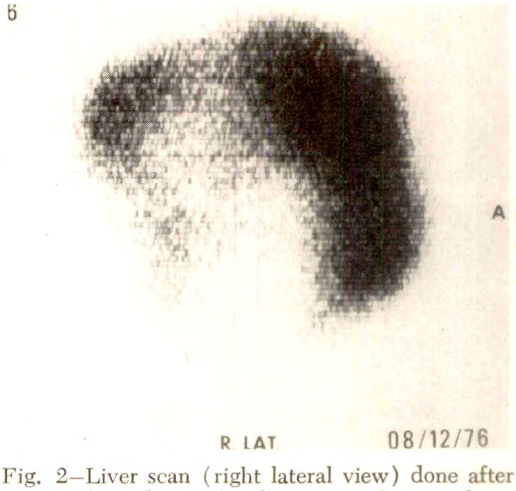


Fig. 2—Liver scan (right lateral view) done after four doses of Adriamycin, showing large filling defect in the right lobe, similar to that seen in Figure 1.

liver scans (Figs. 1 and 2) showed no significant change in the size of the tumor. No significant clinical improvement was seen during Adriamycin therapy; the patient continued to lose weight; right hypochondrial pain and hepatomegaly persisted. Alopecia was evident after the third dose of Adriamycin. In December, 1976 metastatic spread to the lungs was evident on the chest x-ray. The patient died in early February, 1977, about seven months after confirmation of his hepatocellular carcinoma. A postmortem liver biopsy was performed and this showed numerous nodules of poorly differentiated hepatocellular carcinoma in a liver which was obviously fibrotic and cirrhotic. The tumor showed an aggressive appearance with multiple foci of necrosis. There was also considerable cholestasis in the liver parenchyma.

Comment

Hepatitis B surface antigen (HBsAg) has recently been shown to be frequently positive in patients with hepatocellular carcinoma (HCC) in several countries, e.g. Southeast Asia, Africa and Japan.[1-14] The frequency of HBsAg has been reported to be significantly greater in patients with HCC than in normal controls in countries such as Japan, Southeast Asia and Africa, where HCC is particularly prevalent.[3, 6-14] In Western countries such as America, Britain and Australia where the incidence of HCC is low, HBsAg is still significantly higher in patients with HCC than that of controls.[1, 2, 5] In Australia where the incidence of HCC is generally low the occurrence in young adults is even rarer and so the present case is therefore of interest. The occurrence of HCC in the present case, who was a known carrier of HBsAg, adds further support for the association of hepatitis B virus infection and HCC. This association is further supported by the recent finding of familial clustering of HBsAg and HCC.[15, 16] It is also of interest that recently it has been shown that patients with positive alpha-feto-protein have significantly more frequent HBsAg than in controls.[14] Although there is evidence in support of the hypothesis that hepatitis B virus may have some part to play in the causation of hepatocellular carcinoma, the exact role in this virus remains unclear.

Recently it was reported that the drug Adriamycin was effective in reducing the size of the HCC in three out of 11 patients.[17] It was claimed that complete tumor regression was seen in these three cases after two to five courses of Adriamycin treatment. The remission periods were furthermore reported to be from three to seven months.[17] Because of this encouraging report, Adriamycin was given to the present case in an attempt to induce tumor regression. Four courses of Adriamycin were given intravenously to this patient but serial liver scan did not show any significant reduction in tumor size. Several ill-effects like alopecia, nausea and vomiting were noted. The patient survived for about seven months after the diagnosis of the tumor was confirmed by liver biopsy, a period which is comparable to the median survival of eight months previously reported.[17] Double-blind controlled studies will be required before any conclusion can be drawn regarding the value of Adriamycin in HCC.

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Clinical Vignette

Congenital Segmental Absence of Intestinal Musculature

A Rare Cause of Intestinal Obstruction in a Neonate

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Intestinal obstruction due to congenital segmental absence of intestinal musculature in a neonate has been described. This report represents the fifth known case of this abnormality. The defective segment of the bowel was deficient in its muscle coat and consisted only of mucosa, submucosa and serous coats. Exact etiology of the condition is not known but it is presumed that discontinuous myogenesis may be due to some genetic or developmental defect. It is almost impossible to arrive at a preoperative diagnosis. Diagnosis can only be made with certainty at operation by transillumination of the bowel wall and its microscopic examination. Treatment consists of resection of the defective segment of intestine with end to end anastomosis of the normal bowel.

Intestinal atresia and malrotation are among the most common studied causes of intestinal obstruction in our neonatal surgical practice. Recently we have come across a case of intestinal obstruction in a neonate due to congenital segmental absence of intestinal musculature. Review of the literature reveals only four such reported cases of this rare condition.[1-4]

Case Report

In June, 1975, an infant born of a full-term uncomplicated pregnancy and delivery in a multipara was referred to us because of abdominal distention. The neonate was accepting feedings poorly and had not passed any meconium or gas 48 hours after birth. There was occasional vomiting. On examination abdominal distention was evident. Bowel sounds were absent and a vague mass was palpable in the right lower quadrant of abdomen. The anus was well formed and found to be patent on rectal examination. There was no blood or mucus on the examining finger. There was no other congenital abnormality detected. Plain film of the abdomen revealed small bowel obstruction.

An emergency laparotomy was performed after the initial preoperative preparation. Distended loops of small bowel were present. At about the middle of the ileum, ileo-ileal intussusception was seen. The intussusception was reduced but during the process the outer tube burst and, therefore,

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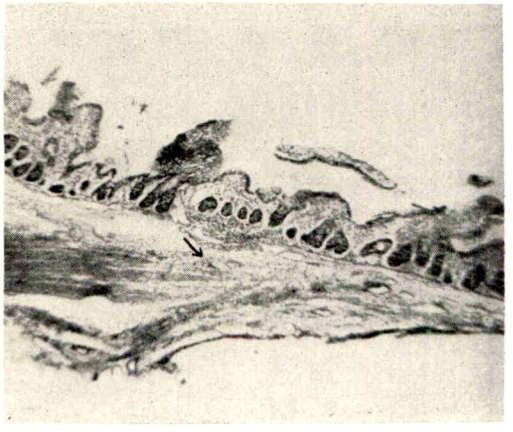


Fig. 1—Photomicrograph showing junction of the normal and abnormal bowel wall. Arrow indicates gradual thinning and cessation of musculature (Hematoxylin and eosin, original magnification x56).



Fig. 2—Photomicrograph showing same field as in Figure 1 under higher magnification (Hematoxylin and eosin, original magnification x140).

intestinal resection with end-to-end anastomosis was performed.

The postoperative course was uneventful.

Pathology

Gross findings:—The resected intestinal segment was 20 cm. long. Towards one end, the intestine was very much dilated and paper-thin. This segment was 8 cm. long and 1 mm. thick. On transillumination, the bowel wall was almost fully transparent. At the two ends of this segment the intestinal wall appeared normal.

Microscopic findings:—Histopathology revealed that the abnormal segment of bowel consisted of mucus, submucus and serous coats with an absence of intervening muscle layers. Section of the normal bowel showed all the bowel wall components. Section at the junction of the normal and abnormal bowel showed a transition from an area having musculature to an area deficient in muscle component (Figs. 1 and 2).

Comment

Neonatal intestinal obstruction due to segmental absence of intestinal musculature is altogether a new entity and was first described by Emanuel, et al[1] in 1967. Since then only three other cases have been reported.[2-4] The present case is the fifth one to be reported.

Atresia can be produced in animals[5, 6] by ligating the bowel and producing a strangulating obstruction or by occluding the mesenteric vessels. It is logical to believe that the effect involves all the layers of the bowel wall. Therefore, any intrauterine catastrophe or vascular accident cannot be supposed to be responsible for the selective segmental absence of intestinal musculature in the present case. It is speculated that this incomplete or discontinuous myogenesis may be due to some genetic or developmental defect.

The development of intussusception can be explained by a mechanism similar to that seen when there is an inherent defect in the neuromuscular co-ordination of the intestine which would allow a localized constriction once formed to persist unduly

and favor invagination into a passive segment of bowel immediately beyond.[7] In the present case we think a muscular segment of the bowel, being an inert and dilated tube, allowed invagination of the proximal contracted segment during intestinal peristalsis.

This rare entity should be considered in the differential diagnosis of neonatal intestinal obstruction. The preoperative diagnosis of this condition would be difficult and could be suggested in a neonate in whom a mechanical cause for intestinal obstruction cannot be found on clinical or radiological examination. Transillumination of the intestinal wall may help in the identification of these a muscular segments at operation. Confirmatory evidence would be forthcoming only after the specimen is examined microscopically.

During the neonatal period such a defect of absent intestinal musculature may cause spontaneous perforation or intestinal obstruction.[1-4]

We believe that such a segment of intestine should be resected and continuity of the normal bowel restored by end-to-end anastomosis.

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Rohtak, Haryana, India

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Clinical Vignette

Ileocecal Valve Prolapse

Confusion with Carcinoma of the Cecum

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Prolapse of the ileocecal valve is a varient which must be differentiated from potentially serious conditions which it can mimic radiologically. Not infrequently, patients have had surgery for a "filling defect" in the cecum only to find a normal or lipomatous valve. Colonoscopy may be of value in differentiating this benign condition from other lesions which would require further intervention.

Case Report

A 57-year old white man was admitted with complaints of vague abdominal bloating and discomfort. He had a history of hemorrhoids with occasional bright red blood on the toilet paper. There was a 4.5 kg. weight loss but no melena or change in bowel habits. He was not anemic. A proctosigmoidoscopic examination revealed only external and internal hemorrhoids. Barium enema examination (Fig. 1) revealed a filling defect in the cecum. The patient underwent colonoscopy which disclosed a prominent but changeable ileocecal valve with prolapse (Figs. 2 and 3). Biopsies of the area disclosed normal colonic mucosa. A repeat barium enema demonstrated complete disappearance of the previously apparent defect (Fig. 4).

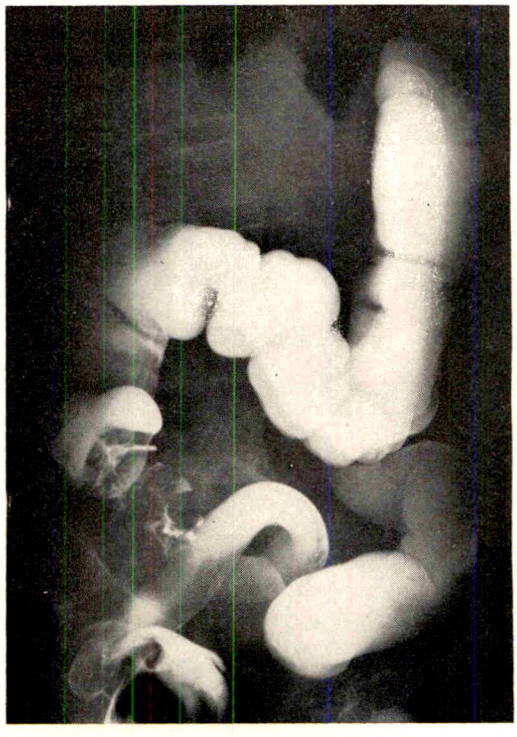


Fig. 1—Radiolucent filling defect in the cecum on barium enema examination.

From the University of Miami School of Medicine and the Department of Medicine, Division of Gastroenterology, Miami Veterans Administration Hospital.

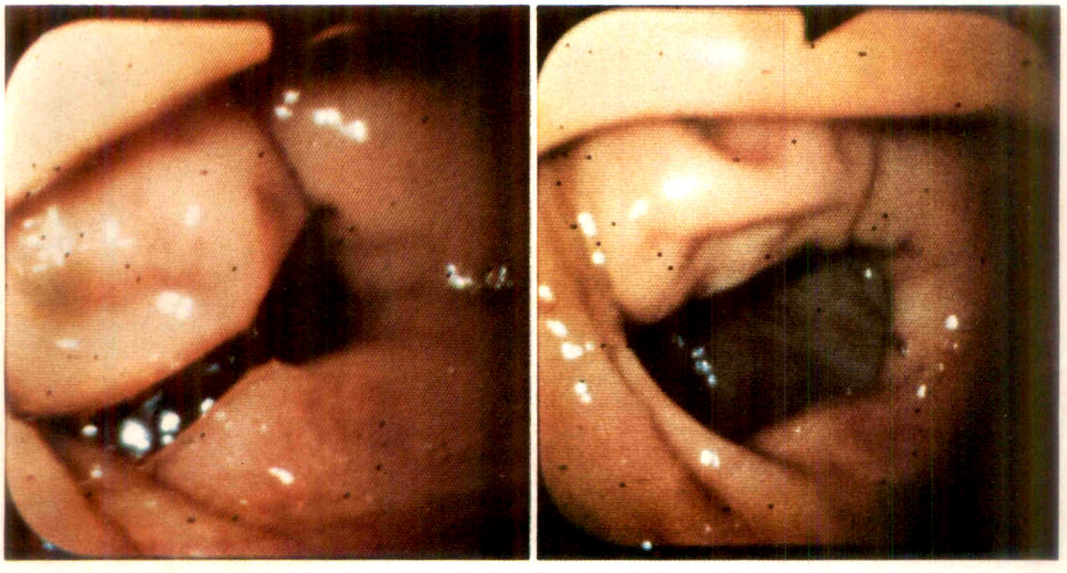


Fig. 2—Smooth mass effect seen on colonoscopy. Overlying mucosa appears intact.
Fig. 3—Similar view showing change in size of ileal opening, and pliability of the valve area.

TABLE I

DIFFERENTIAL DIAGNOSIS OF AN ENLARGED ILEOCECAL VALVE

1. Edema
   a. idiopathic
   b. posttraumatic
2. Hypertrophy—submucosal fatty infiltration
3. Prolapse—herniation of ileal mucosa
4. Tumor
   a. benign—lipoma, carcinoid, fibroma, polyp (adenomatous or villous), endometriosis
   b. malignant—carcinoma, lymphosarcoma carcinoid
5. Inflammatory—Crohn's, ulcerative colitis, tuberculosis, histoplasmosis, amebiasis

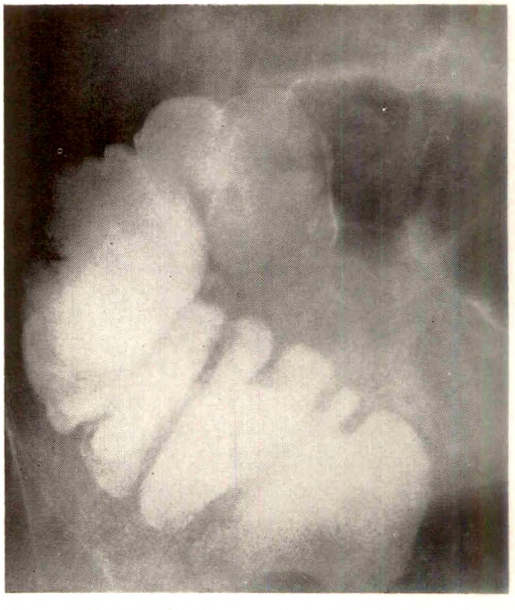


Fig. 4—Repeat barium enema examination showing resolution of the previous defect.

COMMENT

Prolapse of the ileocecal valve occurs in less than 2% of routine barium enema studies.[1] Fleischner and Bernstein[2] studied the correlation between anatomic structures and barium x-ray findings of the ileocecal region using autopsy specimens. They concluded that the valve labia were supported anteriorly and posteriorly by folds or frenula. The upper lip of the valve measured approximately 2 cm. while the lower lips measured 1.5-1.7 cm. Each lip was generally .3-.5 cm. in thickness. More recently, Rosenberg and DiDio[3] have pre-

ferred to call the "valve" a "papilla". They contend that it represents a physiologic sphincter with a conical projection of ileal mucosa into the cecum and that the valve lips are a post mortem artifact. Ileocecal valve, however, remains the commonly used phrase.

The differential diagnosis of an enlarged ileocecal valve is summarized in Table I. Radiographically the normal valve can appear as a translucent shadow with or without a central slit or stellate configuration. Criteria for the radiographic filling defect corresponding to a normal or "hypertrophied" valve with prolapse include an intimate relation of the mass to the valve area, smooth rounded contours to the mass, changes in shape and size with pressure and position (often with herniated ileal mucosa) and lack of obstruction and other changes in the surrounding area. Usually, the normal valve and its variants can be ascertained radiologically with reasonable assurance.

In some cases the radiologist cannot exclude other conditions, particularly carcinoma. In these instances colonoscopy may be useful. At colonoscopy the ileocecal valve is directly visualized. It can be seen to change in size and shape. The opening to the ileum will open and close. The overlying mucosa appears normal and smooth. If substantial fat is present there may be a yellowish tinge. On palpation with a biopsy instrument the valve is soft, compliant and changes in shape readily. Pinch biopsies will reveal normal mucosa.

Ileocecal valve prolapse can occur with a normal or hypertrophied valve. True lipomas (with a well defined capsule) are very uncommon. A syndrome of bloating, right-sided abdominal crampy pain and tenderness with changes in bowel habits has been attributed to valve prolapse but this remains controversial.[4, 5] Occasionally ulcerations can occur on the prolapsed valve. This can result in bleeding and require surgical intervention.[6] Colonoscopy can further define such lesions and prevent surgery on those valves with an atypical radiological appearance which prior to colonoscopy mandated surgery to exclude malignancy.

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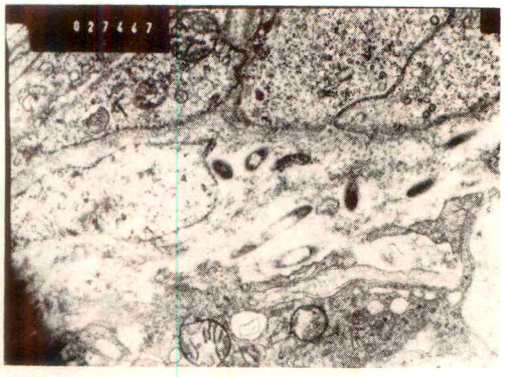


Fig. 4—Electron micrograph of small intestine in Whipple's disease. Large numbers of bacilliform bodies are present in the *lamina propria* (original magnification x43,100).

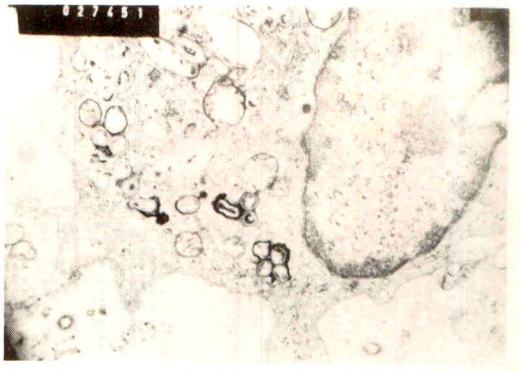


Fig. 5—Electron micrograph of macrophage. Many bacilliform bodies and their remnants are seen (original magnification x33,900).

A peroral small bowel biopsy specimen showed deformed villi (Fig. 2) and foamy macrophages containing PAS-positive material in the *lamina propria* (Fig. 3). Electron microscopy pictures showed bacilliform bodies in the *lamina propria* (Fig. 4). There are many bacilliform bodies in the macrophage (Fig. 5), some of which are disintegrating. One of the bacilliform bodies is showing possible binary fission (Fig. 6). On panendoscopy the mucosa of the second part of duodenum was covered with whitish nodules measuring 2-3 mm. (Fig. 7). The biopsy of these nodules showed typical electron microscopic appearance. The mucosa was also friable with punctate bleeding.

The patient was treated with intramuscular procaine penicillin 600,000 units twice a day, streptomycin 1 gm./day for 15 days. His diarrhea subsided and he gained .45 kg., but d-xylose absorption test two months later was still 2 gm./5 hr. urine.

Tetracycline 250-mg. and penicillin V potassium 250 mg. four times a day by mouth was started. Patient has improved on this regimen.

Comment

The present report provides confirmation of the previously reported occurrence of bacilliform bodies in the active stage of Whipple's disease and the disappearance after antibiotic treatment and clinical remission indicate that the bodies are primary etiologic agents.[6-8] They have been present in all untreated patients studied by electron microscopy. Many organisms were isolated inconsistently in this disease, like coryne bacterium, hemophilus, atypical alpha streptococci and brucella.

In the pathological studies the foamy macrophages contain only traces of lipid and are filled with glycoprotein which reacts strongly with periodic acid Schiff stain. This material was derived from the undigested and essentially indigestible cell walls of the bacilliform bodies[4] and resemble foamy cells of leprosy and the epitheliod cells of tuberculosis containing inclusions which are partly phospholipid in nature.[8]

Kent[10] has pointed out that the predominance of this disease in middle-aged men suggests an unusual host preference by the bacteria. The absence of plasma cells within the *lamina propria* and infiltration of macrophages suggests a defective immunologic response, with deficiency of immunoglobulin which may be an important local factor. But the systemic nature of the disease does not explain this theory.

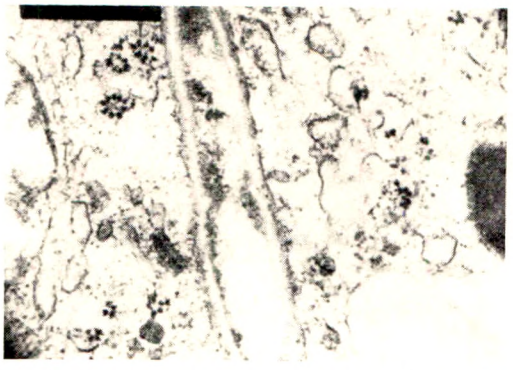


Fig. 6—Electron micrograph of a single bacilliform body demonstrating early binary fission (original magnification x138,500).

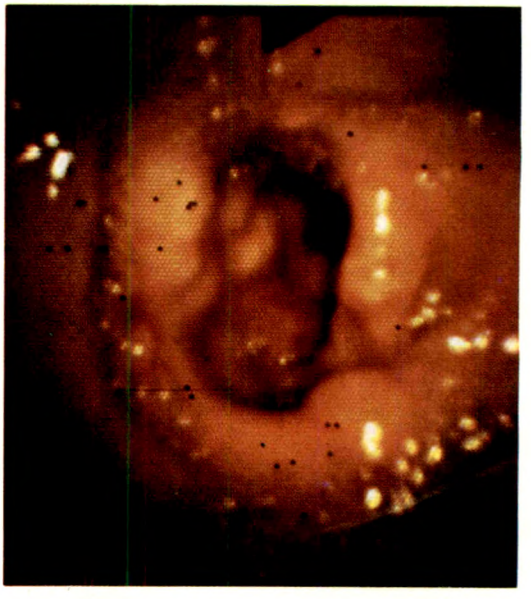


Fig. 7—Endoscopic view of the second part of duodenum. Whitish nodules measuring 2-3 mm. seen.

There is no apparent association of this disease with hypogammaglobulinemias. Intestinal *lamina propria* does appear to be more susceptible along with mesenteric nodes. Portal of entry may be the intestinal lumen but it is not proven.

Fat malabsorption may be due to impediment of progression of chilomicrons by macrophages and may be secondary to obstruction of lymph flow by enlarged mesenteric lymph nodes.[11] The clinical features of Whipple's disease can be simulated by other diseases and the only absolute diagnostic criteria at present are the typical microscopic findings in the small bowel and electron microscopic demonstration of bacilliform bodies. Patients may manifest arthritis, lymphadenopathy, fever, weight loss, hypotension polyserositis. Patients usually have anemia, hypoproteinemia, malabsorption of d-xylose and fat.

Radiologic abnormalities consist of thickened folds and sometimes appear nodular. The duodenum and jejunum are commonly and severely affected. Interstitial edema, PAS-positive macrophages, distention of lymphatics in the *lamina propria* produce swollen, bulbous structures which can explain the radiologic and endoscopic picture. The x-ray differential diagnosis includes intestinal lymphangectasia, amyloidosis. Excessive intestinal secretions are present in lymphangectasia and uniform involvement of jejunum and ileum is present in amyloidosis.[12] In young patients in their twenties and thirties the small bowel x-rays may be normal. Maizel[13] reported seven out of 53 patients had normal small bowel series. Four out of these seven patients were in their twenties.

Gross appearance was reported by Whipple that the mucosa is covered with little pinpoint yellowish grains and red velvety swollen mucosa. Robbins[14] described it as shaggy bearskin rug, Sieracki[1] has described similar appearances in three cases.

Endoscopically Ewers[15] described the picture as minute punctate flecks of white membrane and plaques with bleeding margins and increased friability resembling candida infection. Massarrat, et al[16] described endoscopic picture as white-yellowish pinhead sized knots resembling velvet and in changing densities and also friable

mucosa. Volpicelli, et al[17] described granular yellow-white material respresenting enlarged villi in the second part of duodenum.

Similar appearance was not seen in our endoscopic picture. In addition we have noted 2-3 mm. nodules and friable duodenal mucosa. This may be due to variation in the manifestation of the disease. The nodules are conglomeration of enlarged villi filled with macrophages and glycoprotein.

In the past the disease was always considered fatal. But after the invention of antibiotics this is curable. Many antibiotics were tried with good results. Usual combination is penicillin and streptomycin initially and tetracycline for a prolonged time. Some patients relapse after stopping the antibiotics. Reinstitution of antibiotics achieves the remission. Our patient did not respond well to the penicillin and streptomycin combination, but improved after addition of tetracycline.

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The Radiology Corner*

Phlebectasia of the Small Bowel

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Intestinal phlebectasia is a relatively obscure and therefore little known cause of gastrointestinal bleeding. Although a paucity of cases exists in the medical literature, it is highly probable that its incidence is greater than realized. The following case is reported to stimulate recognition of this entity as a cause of gastrointestinal bleeding and to re-emphasize the importance of small bowel examinations. The radiographic pattern encountered in the small bowel appears unique and quite specific.

Case Report

This 61-year old white male first presented to the Memphis Veterans Administration Hospital in 1961 with complaints of abdominal cramping of four year's duration, associated wtih diarrhea and bright red blood in his stool. Physical examination revealed mild internal hermorrhoids and bilateral lower extremity varicosities. Gastrointestinal evaluation revealed *Strongylo'dosis*, for which he received appropriate therapy and he was discharged.

The patient was readmitted three weeks later with the same complaints except that the stool was now tarry rather than bright red. No evidence of gastrointestinal bleeding was found and he was again discharged.

One year later, he presented with epigastric pain relieved by antacids and with bright red blood in the stool. His condition stabilized in the hospital; he showed no further evidence of bleeding and was sent home.

He returned almost two years later, again with epigastric burning pain, this time relieved with milk. He described intermittent tarry black stools for six months prior to admission. Radiographic evaluation of an upper, small bowel and lower gastrointestinal examination were interpreted at that time as normal. (These are no longer available for review.) The patient underwent an exploratory operation at which time a mesenteric nodal biopsy and incidental appendectomy were performed and a short section of small bowel was resected. During surgery, large vessels were visible on the serosal surface of the small bowel, that were more marked in the jejunum than the ileum (Fig. 1). Microscopic examination of the resected small bowel revealed dilated, engorged veins in the serosa and submucosa with communicating branches

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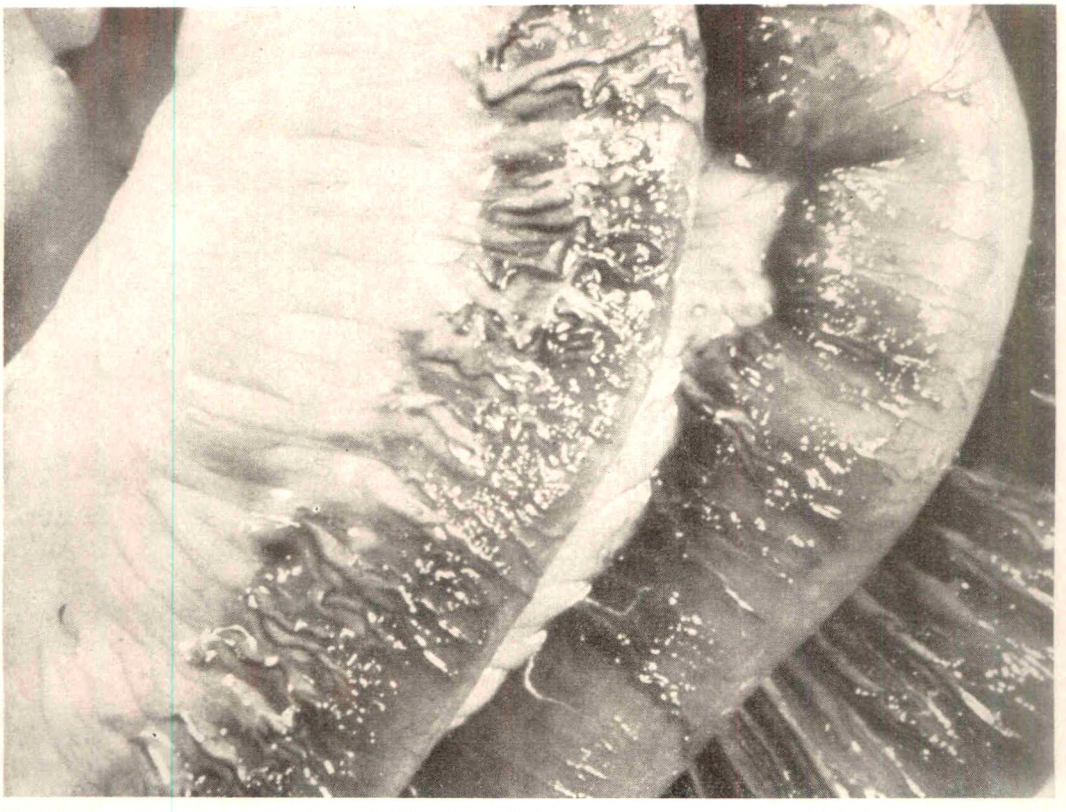


Fig. 1—Gross specimen reveals a slightly distended jejunum, demonstrating dilated veins on its surface.

penetrating the muscularis (Fig. 2). The patient did well postoperatively.

He was readmitted some time later with a two-week history of crampy abdominal pain associated with loose stool. During this time he passed several tarry stools and his hemoglobin was noted to be 9.8%. Small bowel study revealed a diffuse nodulation throughout the bowel (Fig. 3). At laparotomy all but the proximal 12.5 cm. of the jejunum and distal 60 cm. of the ileum were resected. The colon was not involved. Since surgery the patient has been hospitalized several times for gastrointestinal bleeding. All of the episodes have been managed medically. At present, he is retired and living at home.

Comment

Normal connective tissue support diminishes as the tissues of the body age. Consequently, there is a tendency for capillary and venule dilatation to occur in the form of phlebectasia. These lesions are most noticeable in the oral cavity and genitalia but also occur occasionally in the gastrointestinal tract. This combination of multiple phlebectasia has been described by Rappaport and Shiffman,[1, 2] who also noted gastrointestinal bleeding in one patient. It is of interest that either duodenal ulcer or symptoms of peptic ulceration was present in all the patients. The association of peptic disease and phlebectasia may be of definite clinical and pathogenic significance since

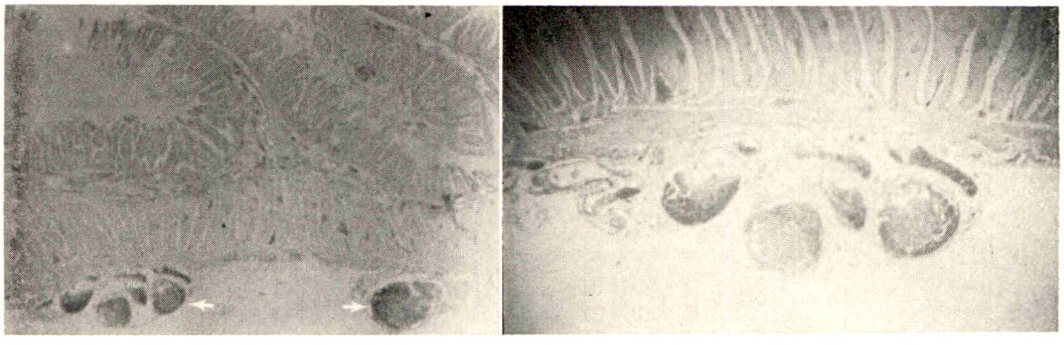


Fig. 2a Fig. 2b

Fig. 2—*Left:* Microscopic section through the jejunum demonstrates several ectatic vessels within the serosa (arrows).
Right: With greater magnification the conglomeration of dilated vessels is better seen.

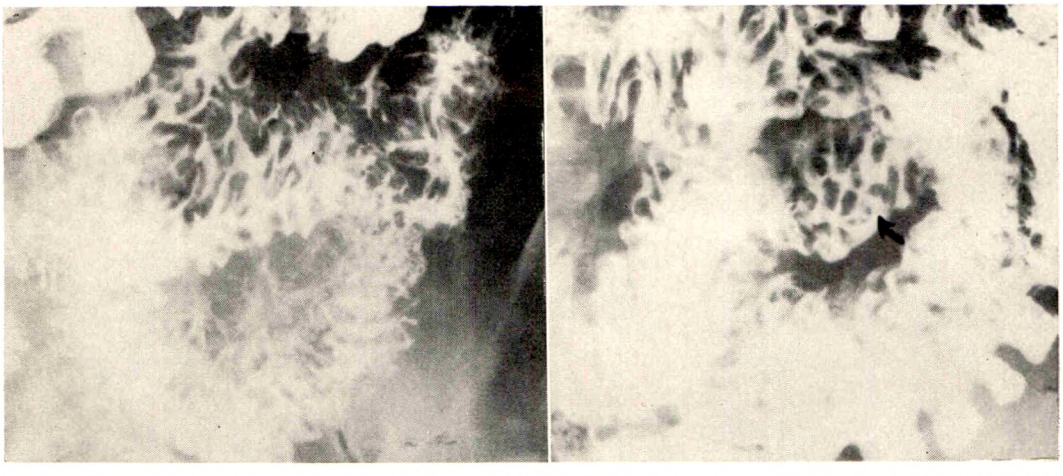


Fig. 3—Parts of small bowel study reveal an irregular nodular pattern with areas that demonstrate a round appearance and others that demonstrate a wormy configuration (arrow).

our patient also presented with recurrent symptoms resembling ulcer disease.

Certain mucocutaneous syndromes manifesting concurrent internal vasular malformations are known to occur. These include the Osler-Weber-Rendu syndrome and the Sturge-Weber syndrome. In the former, A.-V. malformations occur that can be quite extensive resulting in acute hemorrhage.[3]

Similar variceal dilatation in the bowel also occurs in portal hypertension. Pre-existing venous collaterals lying on the surface of the viscera dilate to anastomose with portal tributaries. Localized varices involving the superior mesenteric vein also develop secondary to obstruction by carcinoma of the pancreas or other neoplasms of the gastrointestinal tract. A desmoplastic reaction associated with carcinoid tumor has also been known to occlude multiple tributaries of the mesenteric vein causing dilation of these vessels. None of the above lesions were present in our patient and the oral and scrotal changes noted in Rappaport and Shiffman's series of patients also were not seen. Rather, short of laparotomy,

the only evidence of phlebectasia was that noted on the small bowel barium studies.

The mucosal pattern of the small bowel consists of multiple smooth curvilinear and nodular, filling defects of approximately uniform size. The bowel may be slightly dilated but no ulceration or mucosal destruction is apparent. When the filling defects are arranged transverse to the longitudinal axis of the gut they appear linear and when viewed end on they appear nodular. Close observation, however, will reveal a winding, wormy pattern that strongly resembles the commonly encountered varices in the esophagus (Fig. 3). This pattern, when seen, is characteristic and diagnostic. Angiography could be most revealing but unfortunately it was not performed. In all likelihood dilated ectatic vessels would appear during the venous phase.

Although the pattern of phlebectasia appears distinctive, it must be distinguished from other lesions that give rise to nodular changes within the small bowel. These include mastocytosis, lymphosarcoma, intestinal lymphangiectasia and Crohn's disease.[4] Phlebectasia is easily distinguished from Crohn's disease because of the absence of inflammatory changes, e.g. strictures, ulceration, rigidity and separation of bowel loops. Polypoid lesions in the stomach are far more typical for the Cronkite-Canada syndrome. Nodular defects are unusual in lymphagiectasia and the bowel is usually wet due to excessive mucosal secretions. Mastocytosis and Whipple's disease demonstrate nodular defects but the latter more often reveals a relatively wild pattern consisting of segmentation and excessive mucosal secretions. Waldenstrom's macroglobulinemia can produce diffuse nodularity but is readily identified by the characteristic serum electrophoretic and immunoelectrophoretic patterns. The filling defects produced by lymphosarcoma vary in size and may be associated with central ulceration and changes in bowel caliber. Nodular lymphoid hyperplasia is distinctly nodular and is often associated with altered immunoglobulins.

Conclusion

All too commonly, the small bowel study utilized for evaluating the gastrointestinal tract is superficial. In cases where no obvious upper gastrointestinal or colonic cause of bleeding is found, the bleeding site(s) may well be in this part of bowel and careful scrutiny of the mucosal pattern can be revealing. Small bowel phlebectasia is an uncommon cause of bleeding but demonstrates certain radiographic features that enable one to render a specific diagnosis.

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The Last Page

Questions in Gastroenterology

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The Last Page appears as a regular feature in each issue of The American Journal of Gastroenterology.

The questions that follow have been prepared exclusively from material in the current issue of the Journal and the page on which the answer can be found is indicated with each question.

One way for regular readers of the Journal to utilize this feature is to scan *The Last Page* and attempt to answer the questions before reading the Journal. Then, when the articles have been read, return to *The Last Page*, again try to answer the questions and finally refer to the page locations that are provided in order to confirm your an-

For each question, one or more responses may be correct, or none may be correct.

1. CYTOLOGICAL DIAGNOSIS OF DIGESTIVE CANCER:

   A. Is especially useful in the presence of stenotic lesions of the esophagus and colon in which biopsy is not technically feasible.

   B. Can be used to screen large populations at risk.

   C. Must be done by direct endoscopic abrasion as direct washings give very poor results.

   D. Should be performed before biopsy which might interfere with cytological sampling.

   (Page 359)

2. PRIMARY NEUROPATHIC AMYLOIDOSIS:

   A. Is inherited as a Mendelian recessive trait in northern English fisherman.

   B. Is chiefly manifest as a neuropathy of peripheral and autonomic nerves.

   C. Can cause obstipation, diarrhea and loss of anal sphincter control.

   D. May be complicated by malabsorption.

   (Page 365)

3. PANCREATITIS COMPLICATING PREGNANCY:

   A. Is rare.

   B. Usually occurs in the third trimester or early puerperium.

   C. Has been shown in humans to be due to a hypersecretory state.

   D. Is usually due to alcohol abuse.

   (Page 371)

4. THE RESULTS OF INTRAVENOUS ADMINISTRATION OF A SYNTHETIC PROSTAGLANDIN E_2 ANALOG ON THE PAROTID GLAND IN THE DOG ARE:

   A. Inhibition of fluid and electrolyte secretion.

   B. Stimulation of amylase output.

   C. Similar to those seen with administration of PGF_2.

   D. Definitely due to reduced blood flow rather than to a primary effect on the secretory cells.

   (Page 377)

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5. IATROGENIC ESOPHAGEAL PERFORATION DIFFERS FROM SPONTANEOUS PERFORATION IN THAT:

A. The mortality is significantly lower.

B. The event is recognized earlier in these frequently hospitalized patients.

C. The patients undergoing instrumentation are usually fasting.

D. The injury is often blunt and less forceful giving a greater chance for confinement to the mediastinal space.

(Pages 380, 381)

6. CHRONIC ACTIVE HEPATITIS:

A. Like acute hepatitis has been shown to have an increased incidence of malignancy of the cervix.

B. Should not be treated with immunosuppressive therapy for more than two years due to the risk of malignancy.

C. Rarely requires long-term therapy.

D. Requires therapy with potent drugs where the risk of treatment must be balanced against the risk of the patient's disease.

(Page 383)

7. ACETAMINOPHEN HEPATOTOXICITY:

A. Is mild after ingestion of about 10 gm.

B. Is severe only after a 15-20 gm. overdosage.

C. Is potentiated by the use of alcohol and barbiturates that induce hepatic microsomal cytochrome P450 mixed function oxidase.

D. Is prevented when glutathione binds the toxic metabolite and forms nontoxic mercapturic acid which is excreted in the urine.

(Page 388)

8. HEREDITARY HEMORRHAGIC TELANGIECTASIA:

A. Is not seen in black patients.

B. Is a familial disease characterized by mucosal surfaces containing telangiectases which are thin walled and fragile.

C. Commonly presents with epistaxis or gastrointestinal bleeding.

D. Is inherited as an autosomal recessive.

(Page 390)

9. IN PATIENTS WITH A CHOLEDOCHAL CYST:

A. The classical triad of pain, jaundice and a palpable right upper quadrant mass is seen over 80% of the time.

B. Accuracy of diagnosis by I.V.C. is inversely proportional to the degree of jaundice present.

C. The surgical procedure of choice is usually a choledochocystojejunostomy.

D. Biliary cirrhosis may develop.

(Page 395)

10. HEPATITIS B SURFACE ANTIGEN:

A. Is frequently positive in patients with hepatocellularcarcinoma (HCC).

B. Is significantly higher in patients with HCC than in controls only, in countries where HCC is particularly prevalent.

C. Is seen more frequently in patients with positive alpha-feto-protein than controls.

D. May be present in familial clustering with HCC.

(Page 399)

11. INTESTINAL OBSTRUCTION IN THE NEONATE CAN BE DUE TO:

A. Intestinal atresia.

B. Malrotation.

C. Congenital segmental absence of intestinal musculature.

D. Intussusception.

(Page 401)

12. PROLAPSE OF THE ILEOCECAL VALVE:

A. Occurs in less than 2% of routine barium enema studies.

B. Can occur with a normal or hypertrophied valve.

C. Certainly leads to the syndrome of bloating, right-sided abdominal cramping pain and tenderness with changes in bowel habits.

D. Can ulcerate resulting in bleeding.

(Page 406)

13. IN WHIPPLE'S DISEASE:

A. PAS positive macrophages must be found in biopsy material from the small bowel to establish the diagnosis.

B. Bacilliform bodies present in the active stage disappear after antibiotic treatment and clinical remission.

C. Patients usually have anemia, hypoproteinemia and malabsorption of d-xylose and fat.

D. There is an association with hypogammaglobulinemias.

(Page 410)

14. SMALL BOWEL PHLEBECTASIA:

A. Produces distinctive multiple smooth curvilinear and nodular filling defects of approximately uniform size in the small bowel.

B. May coexist with lesions of the oral cavity and scrotum.

C. Can cause significant gastrointestinal bleeding.

D. Is another name for the Osler-Weber-Rendu syndrome.

(Page 414)

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BOOK REVIEWS FOR GASTROENTEROLOGISTS

Crohn's Disease: by Bryan N. Brooke, M.D., David R. Cave, M.D., John F. Gurry, M.D. and Denis W. King, M.D. 113 pages, illustrated. Oxford University Press, New York, N. Y., 1977, Price $21.00.

This book, published by the Oxford University Press, is edited by Bryan Brooke, Professor of Surgery at St. George's Hospital, David Cave, British Digestive Foundation Research Fellow, John F. Gurry, Lecturer in Surgery at St. George's Hospital and Dennis W. King, Registrar in Surgery at St. George's Hospital, London, England. This Small monograph, 113 pages in length, is beautifully written and well laid out. Its most interesting sections are those on the etiology of disease. This is an area in which the major authors have made substantial scientific contributions. The authors, in fact, were able to transmit Crohn's disease or a disease very similar to it to New Zealand white rabbits. The objective findings were ileal thickening, mucosal ulceration, pericolic abscess and lymph node enlargement. Furthermore, they were able to pass this "disease" to a second generation of rabbits by intravenous or intraileal injections of a filtrate of mesenteric lymph nodes or cecum from the primary rabbits. As they so clearly point out the key to all studies is a slowly evolving granulomatous response in either mice or rabbits. Earlier studies had failed to follow the animal model for a sufficiently long time.

The book is basically subdivided into eight separate chapters: etiology, genetics, epidemiology, clinical features, acute complications, diagnosis, management and a special chapter on Azathioprine which has been of particular interest to this particular group. The authors have covered the subject of Crohn's disease well and clearly in this book with a good review of the literature and a complete summary of their own particular interests such as etiology, acute disintegrative colitis, Crohn's disease of the colon anl the use of Azathioprine. It is to be recommended to all gastroenterologists, and surgeons interested in this complex and enigmatic disease.

ADRIAN J. GREENSTEIN, M.D., F.A.C.G.

Developments in Digestive Diseases, 1st edition: by J. Edward Berk, M.D., F.A.C.G. 199 pages, illustrated. Lea & Febiger, Philadelphia, Pa., 1977. Price $22.50.

This is the first in the series to be edited by Dr. J. Edward Berk. Judging by it as a sample it should be very useful in keeping the clinician and general practitioner up-to-date. This volume covers gastrointestinal endoscopy, the lower esophageal sphincter, treatment of duodenal ulcer, gastrointestinal hemorrhage, hepatitis viruses, CAT, sonography, gastrointestinal gas, etc. The contributors are first rate and have jammed an awful lot of what's new into the book.

DAVID A. DREILING, M.D., F.A.C.G.

Infectious and Parasitic Diseases of the Intestine, Discussions in Patient Management: by Hobart A. Reimann, M.D. and Kerrison Juniper, Jr., M.D. 115 pages, illustrated. Medical Examination Publishing Co., Inc., Flushing, N. Y., 1977. Price $8.00.

Hobart A. Reimann is Professor of Medicine at the Hahnemann Medical College and Hospital of Philadelphia and Kerrison Juniper is Professor of Medicine and Chief of the Gastrointestinal Division of the Southern Illinois University School of Medicine in Illinois. This loose leaf book summarizes the various infectious and parasitic intestinal diseases giving a brief review of each. It is divided into two parts. Part 1 deals with viral, bacterial and mycotic dysenteries and Part 2 deals with diarrheas caused by protozoa and metazoa. Each section consists of a discussion of the etiology, epidemiology, symptoms and diagnosis in logical order followed by prevention and treatment. There are numerous tables in the book which are useful for recall of information. The end of the book has a section on antiparasitic drugs and a general index. There is a small section on enterocolitis after surgery and associated obstructive enteric diseases such as ulcerative colitis, regional enteritis and pseudomembranous colitis. In such a short book a detailed analysis of each topic cannot be given. However, the salient features of each topic are considered in a brief and succinct form. This is a useful book for quick reference for practicing physicians and will also be of value to those preparing for examinations such as final medical examination or the flex examination. The information in general is accurate and the major drugs used in each infection are summarized in the tabular consideration of the different diseases given towards the end of each section.

ADRIAN J. GREENSTEIN, M.D., F.A.C.G.

Complications of Gastric Surgery: by David Fromm, M.D. 163 pages, illustrated. John Wiley & Sons, Inc., Somerset, N. J., 1977.

This brief 160 page book is from the Clinical Gastroenterology monograph series edited by John M. Dietschy. It is written by David Fromm, Associate Professor of Surgery at Harvard Medical School and Beth Israel Hospital, Boston.

It is an excellent review of the current literature and conveys to the reader the most recent developments in this area. All major complications of gastric surgery from weight loss, through afferent and efferent loop obstruction, dumping, reflux gastritis to carcinoma, are thoroughly reviewed in the 17 separate chapters.

The text is clear, and the bibliography at the end of each chapter complete. It will be an asset to all those involved in treating the postgastrectomy patient especially the surgeon, the gastroenterologist and the internist.

ADRIAN J. GREENSTEIN, M.D., F.A.C.G.

Diseases of the Gallbladder and Biliary System: by Leslie J. Schoenfield, M.D. 362 pages, illustrated. John Wiley & Sons, Inc., Somerset, N. J., 1977.

This monograph, devoted principally to gallstone disease, was written by Dr. Leslie J. Schoenfield, one of the pioneers in the field of gallstone research and Chief of Gastroenterology at the Cedars-Sinai Medical Center in Los Angeles, CA. The chapter of surgical treatment of biliary diseases was written by Dr. Frank G. Moody, a distinguished surgeon, now a chairman at the Department of Surgery of the University of Utah in Salt Lake City.

It is undoubtedly the most complete, the most up-to-date, and authoritative review of diseases of the biliary system. It comes at a very opportune time because of the high prevalence of gallstone disease, its socioeconomic implications and the newly developed methods for chemical dissolution of cholesterol stones.

This monograph integrates scientific and clinical concepts with unique precision and clarity and is addressed to a vast readership of clinical gastroenterologists, gastroenterological surgeons and investigators in the field of cholelithiasis.

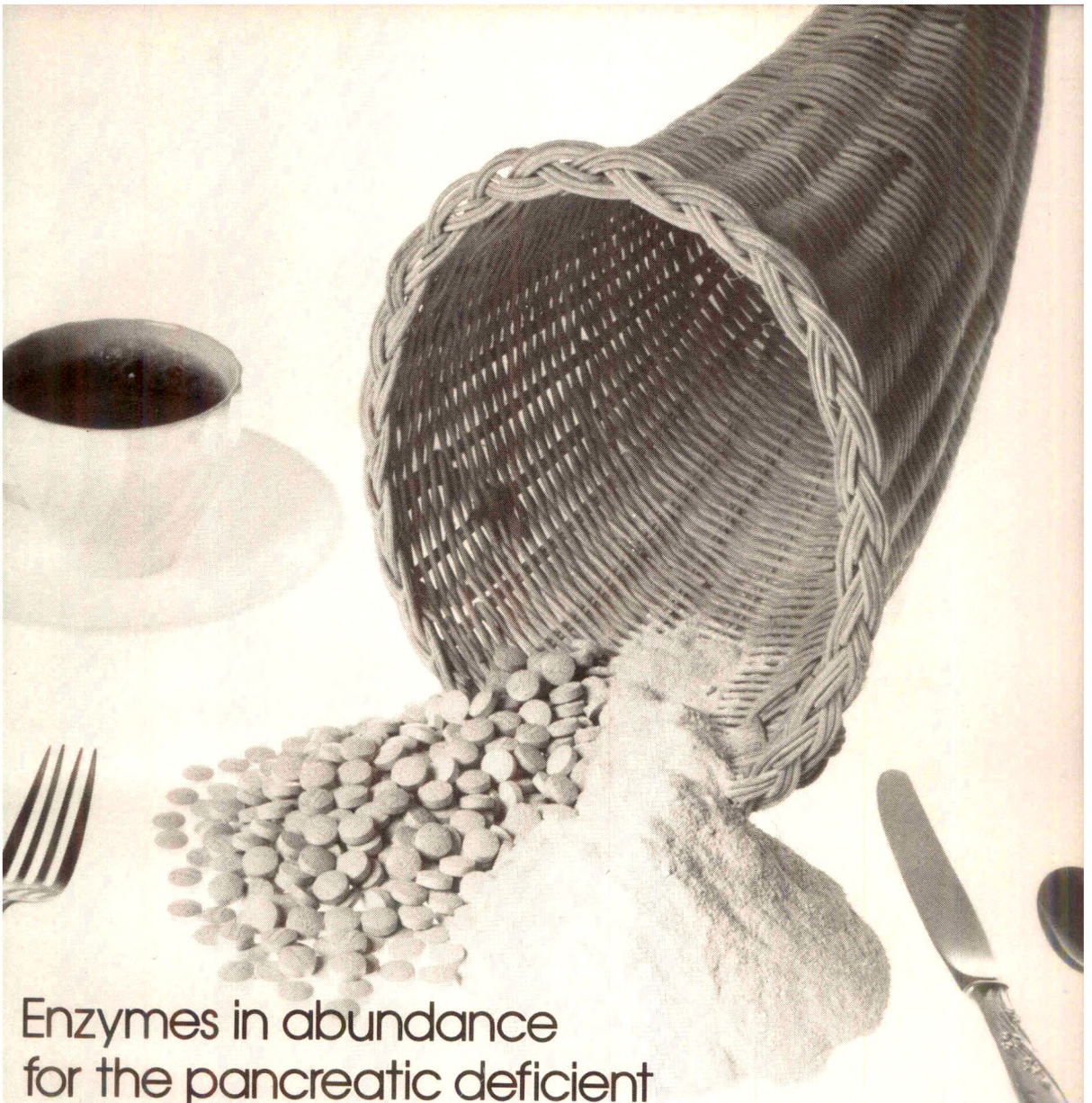
It is likely to remain a key source of reference on biliary diseases for many years to come.

DEMETRIUS PERTSEMLIDIS, M.D., F.A.C.G.

Case Studies in Therapeutic Nutrition: by Barbara Luke. 143 pages. Little, Brown & Co., Boston, Mass., 1977. Price $5.95.

This is the third text in the series of continuing education for nurses. This book integrates nursing and nutrition and illustrates the importance of both in therapeutic regimens. It is subdivided into three sections which consider proteins, fats and carbohydrates. A method of utilization is given in the introduction which considers modifications of each of these three major dietary groups with special emphasis on renal disease, hepatic disease and cancer of the gastrointestinal tract in the case of dietary proteins; on pancreatic disease and gastrointestinal surgery in the case of modification of dietary fat and diabetes mellitus with particular reference to carbohydrates. A rather unique method of study is attempted in this book in which the case histories and pathophysiology of dietary and drug therapy are considered in relationship to each of the clinical symptoms suffered by the patient. This book certainly has an imaginative approach to the teaching of disease based on a study of patient histories and is to be highly recommended to all nurses interested in the pathophysiologic basis of various aspects of nutrition. They will also benefit from a deeper understanding of the physiology of clinical symptoms and an attempt to integrate this with the total nutrition of the patient. It will also be of value to physicians interested in nutrition and to medical students attempting to understand more about the nutritional physiology of the body.

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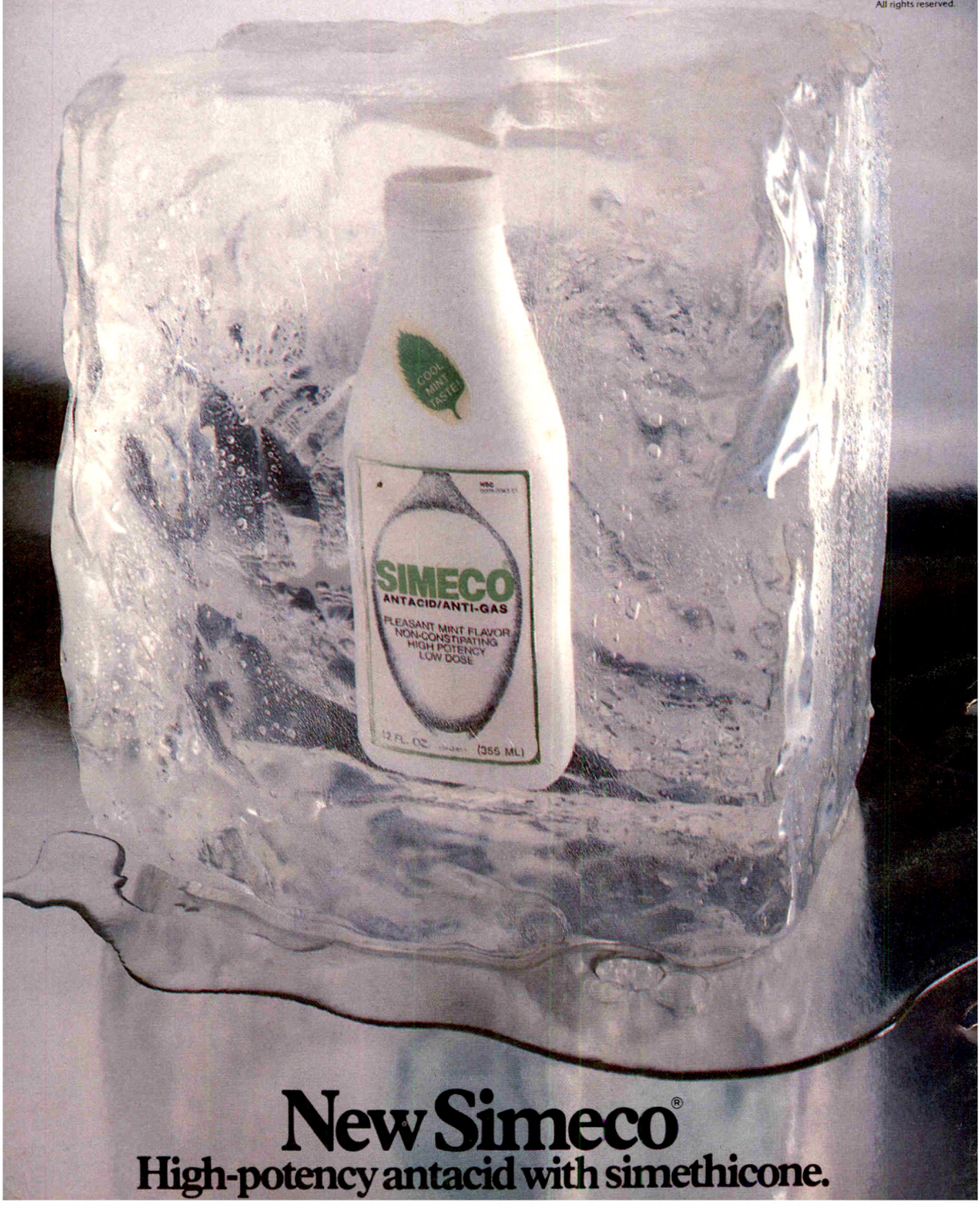
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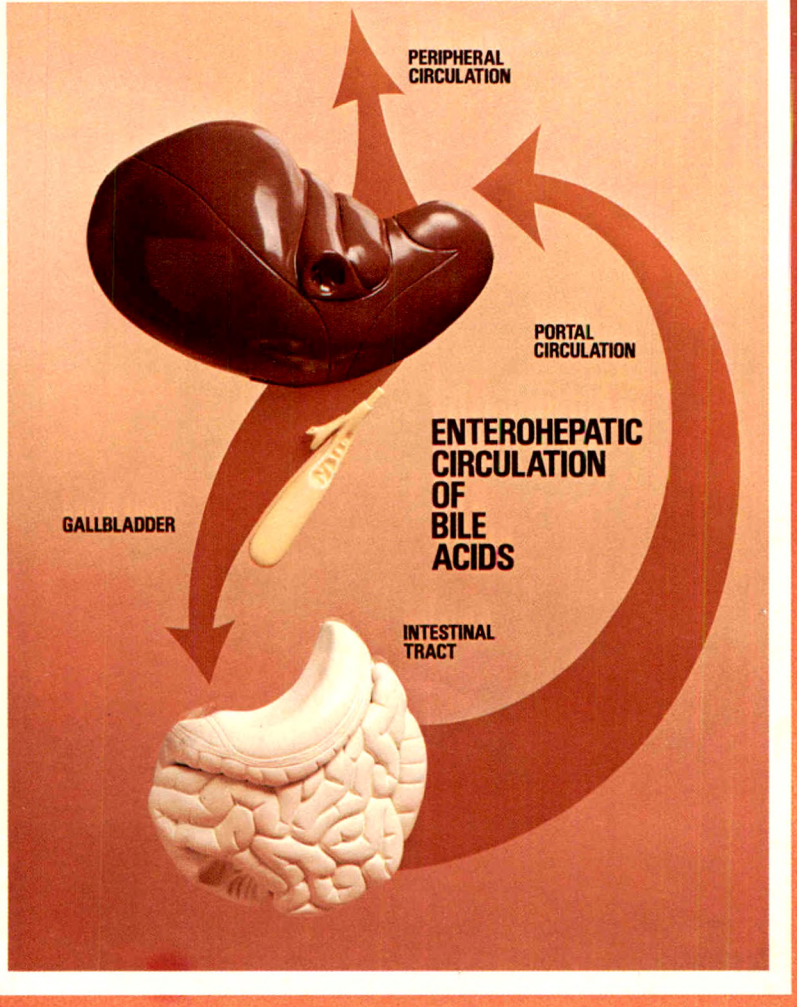
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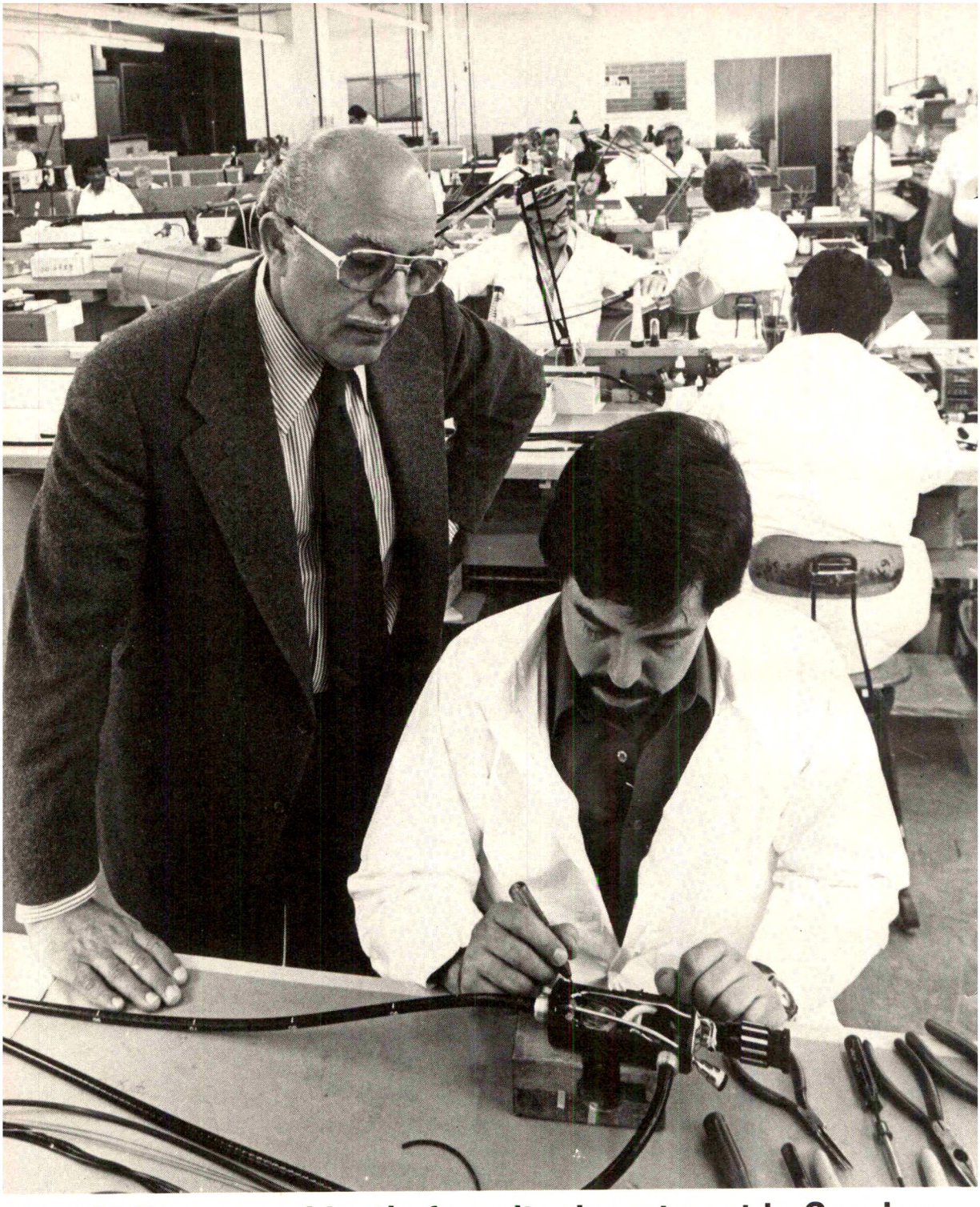
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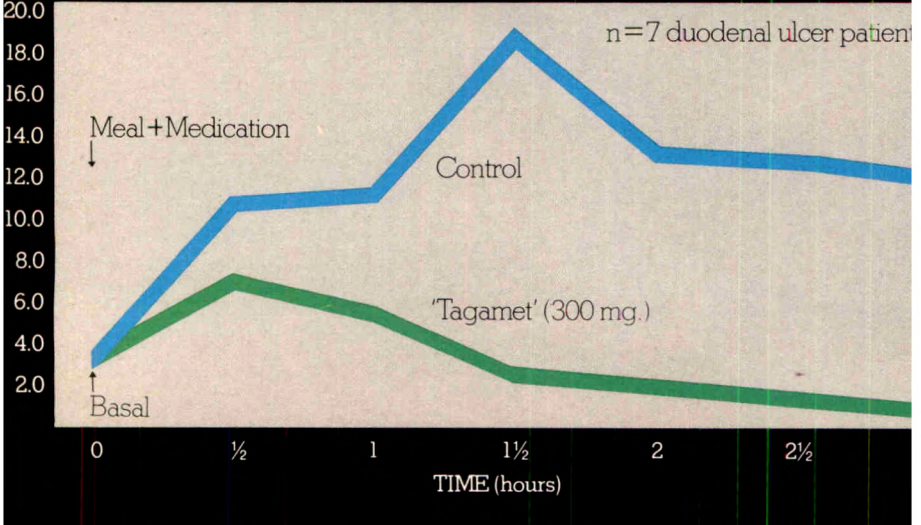
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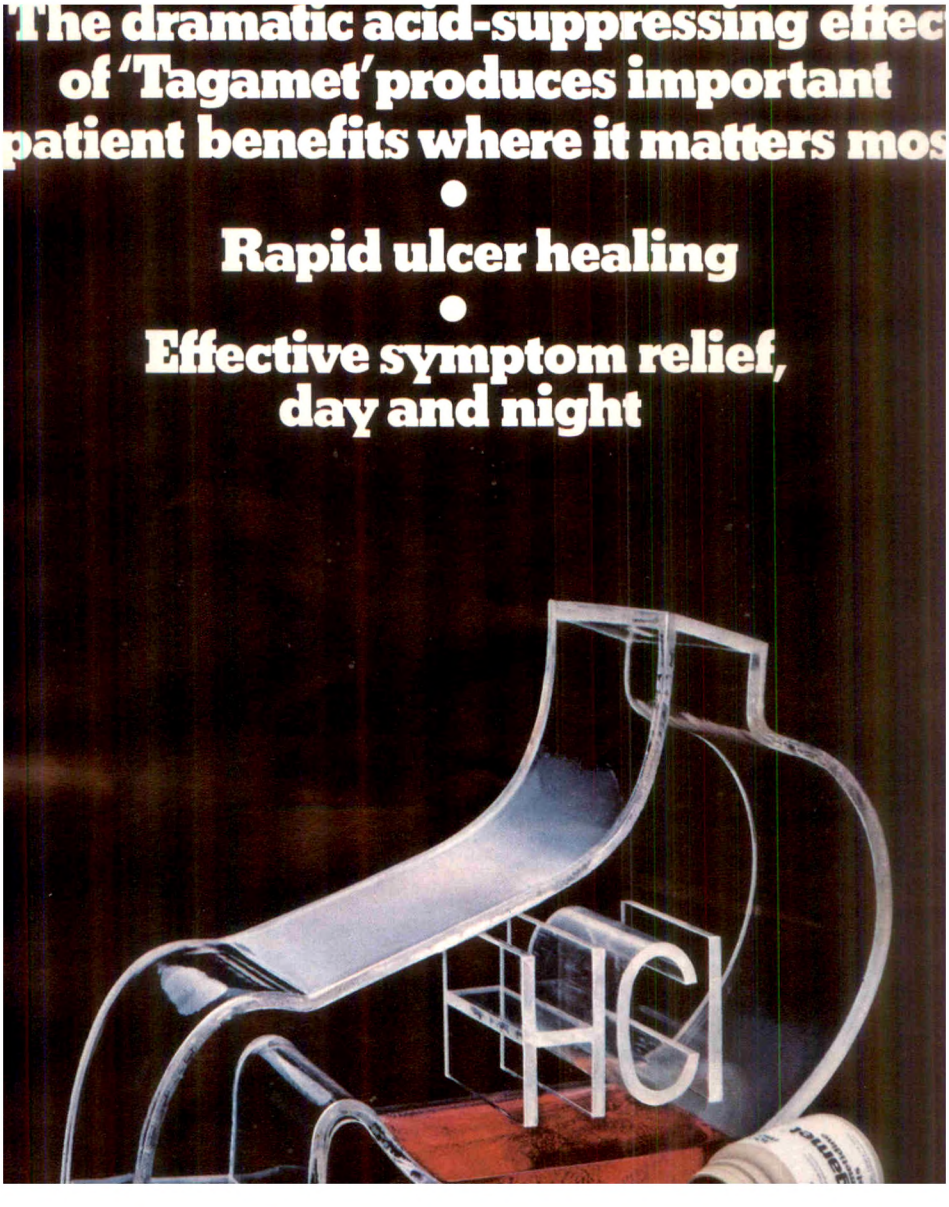
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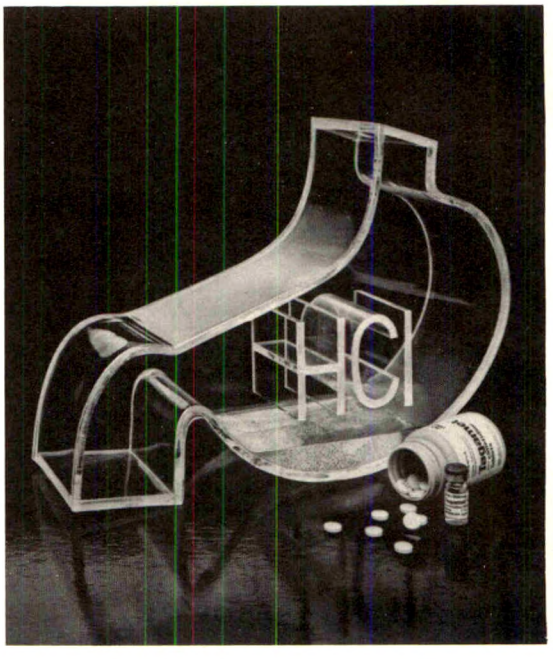

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Lack of experience to date precludes recommending 'Tagamet' for use in pregnant patients, women of childbearing potential, nursing mothers or children under 16 unless anticipated benefits outweigh potential risks; generally, nursing should be discontinued in patients taking the drug.

Symptomatic response to 'Tagamet' therapy does not preclude the presence of a gastric malignancy.

Adverse Reactions: Diarrhea, muscular pain, dizziness, rash, mild gynecomastia. A few cases of reversible confusional states have been reported, usually in elderly and/or severely ill patients. A few cases of neutropenia have been reported, but no causal relationship could be established. Increased serum transaminase and creatinine, as well as rare cases of reversible fever and interstitial nephritis, have been reported; these cleared on withdrawal of the drug.

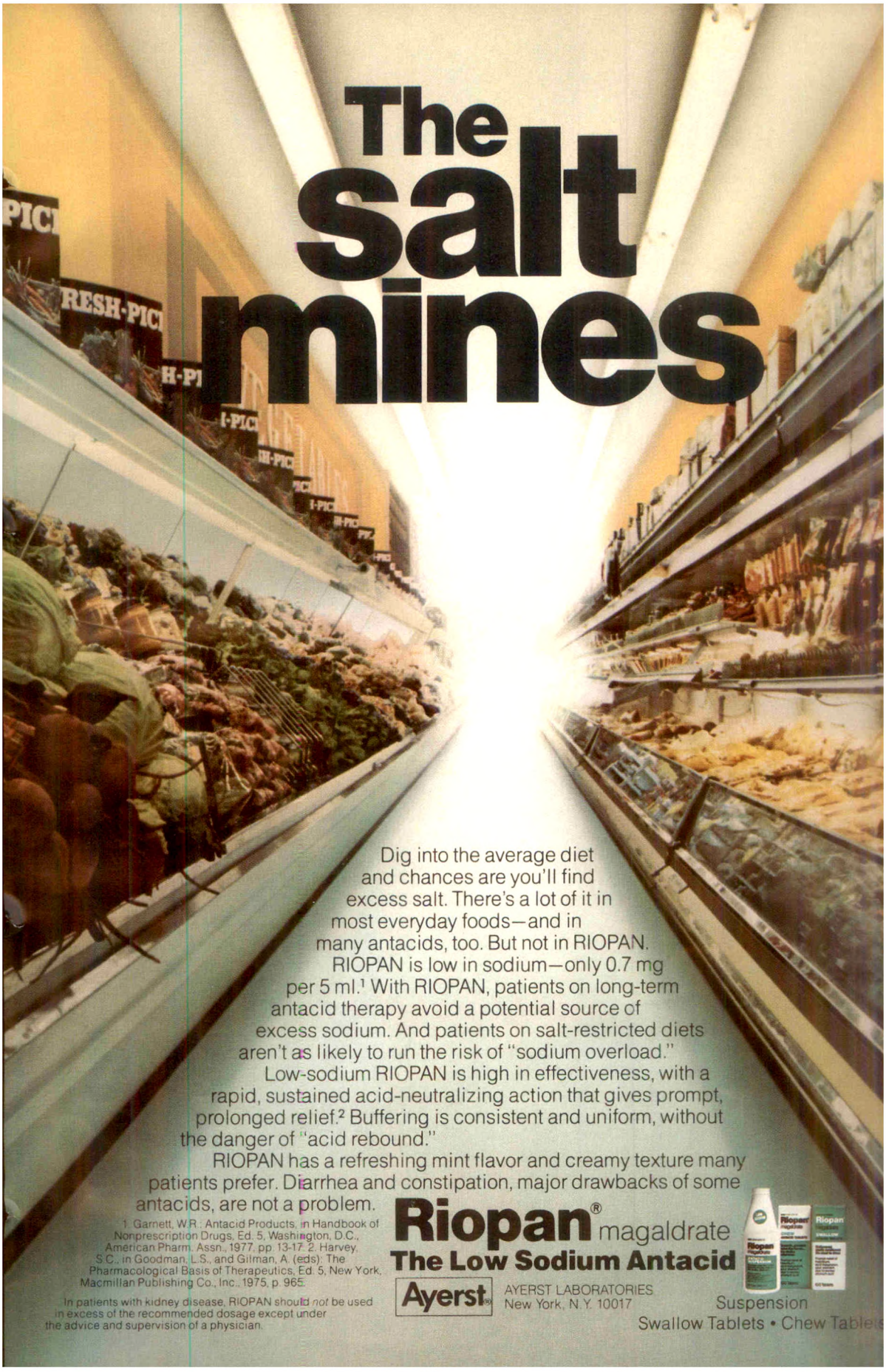
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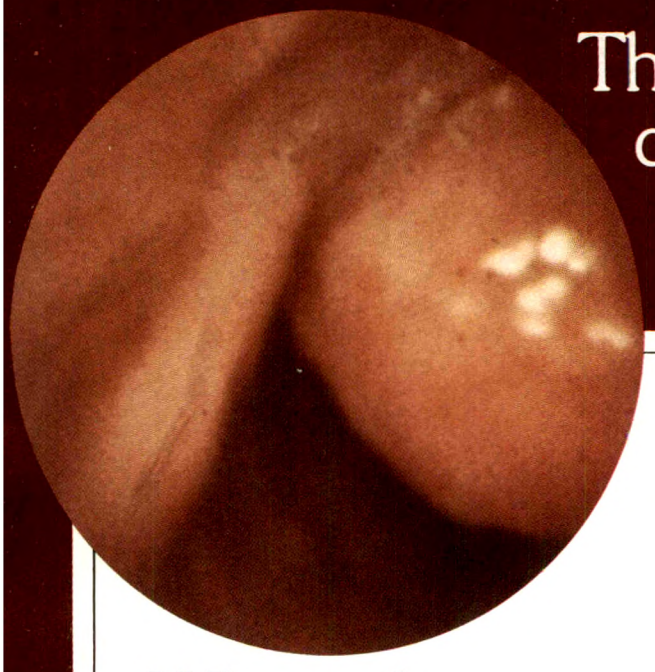
1. Garnett, W.R.: Antacid Products, in Handbook of Nonprescription Drugs, Ed. 5, Washington, D.C., American Pharm. Assn., 1977, pp. 13-17. 2. Harvey, S.C., in Goodman, L.S., and Gilman, A. (eds): The Pharmacological Basis of Therapeutics, Ed. 5, New York, Macmillan Publishing Co., Inc., 1975, p. 965.

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Physical exam is unrevealing. X-ray studies are inconclusive.

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Esophagoscopy was performed, and a round submucosal tumor thought to be a *leiomyoma* was identified at the level of 28 cm from the incisor teeth. The patient refused surgical intervention.

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Case discussion based on *The Clinical Significance of Esophagoscopy* by Bernard M. Schuman, M.D., one in a series of monographs made available by Roche Laboratories in fulfillment of its commitment to continuing education in gastroenterology. This case history illustrates the diagnostic use of endoscopy: it does not represent an indication for Librax therapy.

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-confirmatory or contradictory-

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Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established.

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MEETINGS OF INTEREST

44th Annual Convention, American College of Gastroenterology, Disneyland Hotel, Anaheim, CA, 22-24 October 1979.

Annual Course in Postgraduate Gastroenterology, American College of Gastroenterology, Disneyland Hotel, Anaheim, CA, 25-27 October 1979.

International Conference on Digestive Diseases, Postgraduate Course co-sponsored by the American College of Gastroenterology, the University of South Florida Medical School in Tampa and the Florida Hospital in Orlando. Dutch Inn, Lake Buena Vista, FL, 28-30 January 1979.

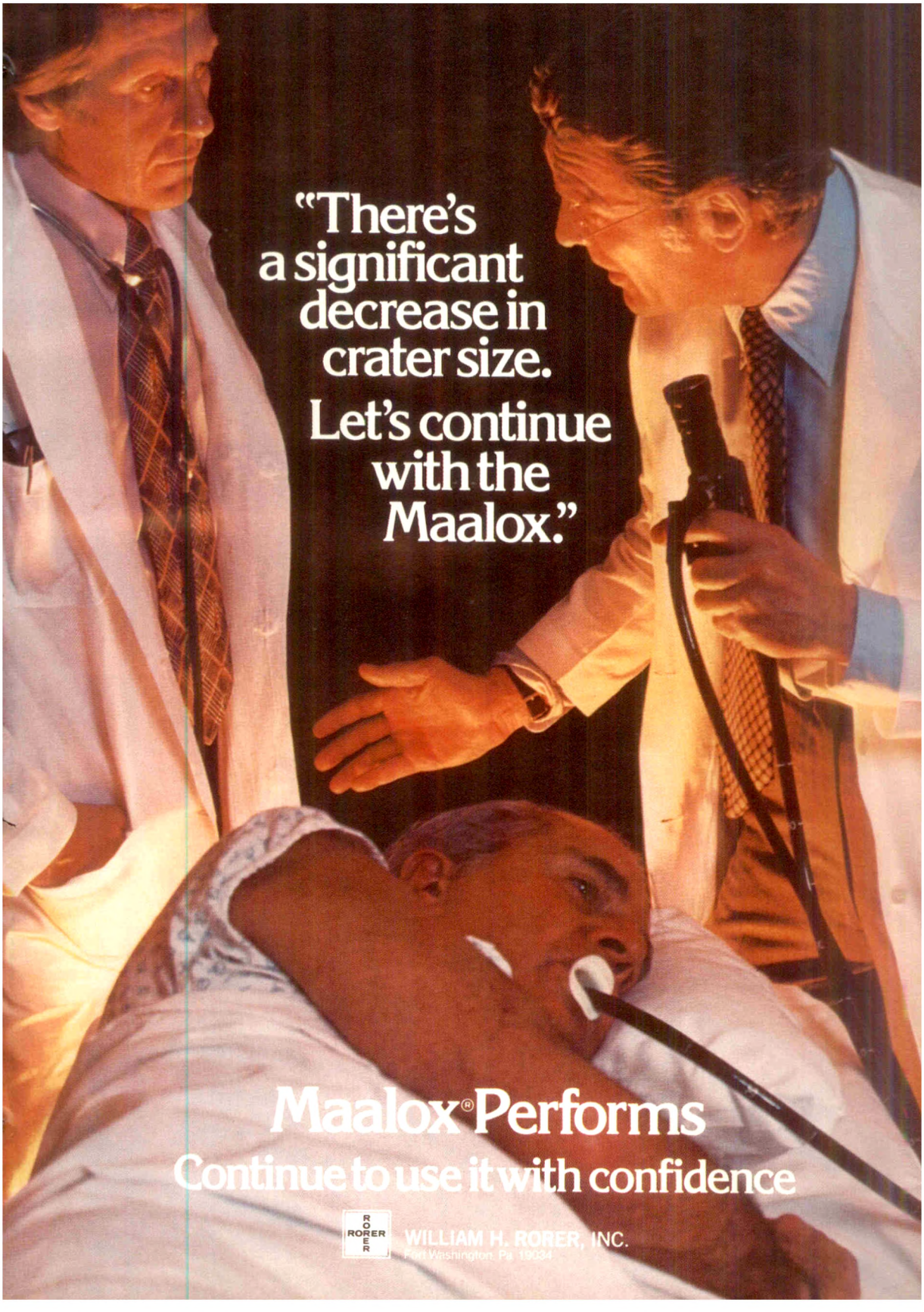
Current Concepts, Controversies and Clinical Strategies in Gastroenterology, Cedars-Sinai Medical Center Departments of Gastroenterology and Medical Education, Century Plaza Hotel, Los Angeles, CA, 12-15 February 1979.

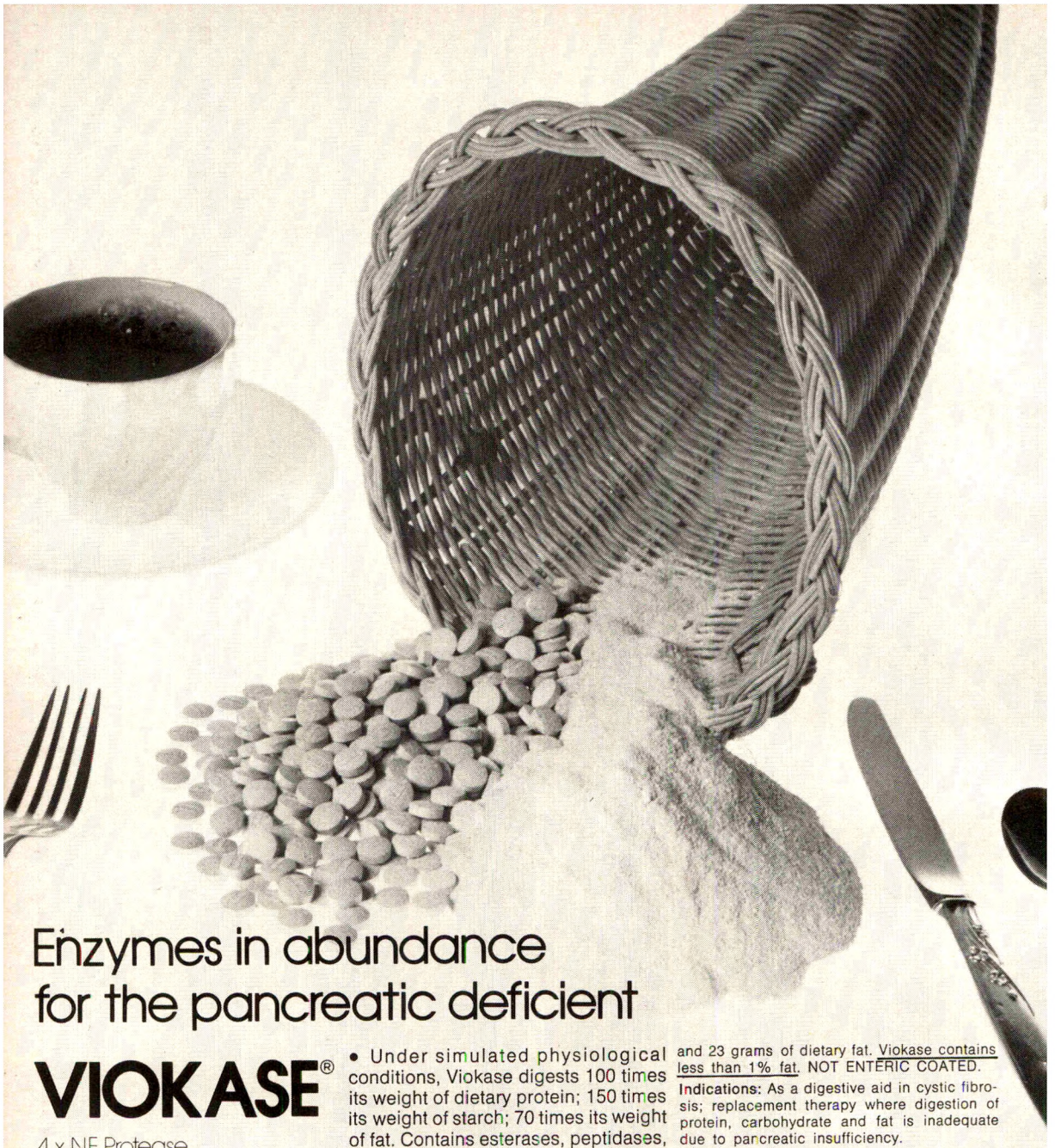
A Symposium on Gastroenterology, University of California School of Medicine, San Francisco and the Central California Committee for Gastroenterology, Ahwahnee, Yosemite National Park, CA, 11-14 March 1979.

Eighth Annual William Beaumont Gastrointestinal Symposium, William Beaumont Army Medical Center, El Paso, TX, 21-23 March 1979.

Inflammatory Bowel Disease: Experience and Controversy, Teaching Seminar co-sponsored by the American College of Gastroenterology and Lenox Hill Hospital, Einhorn Auditorium, Lenox Hill Hospital, New York, NY, 20, 21 April 1979.

A Day in the G.I. Tract—An Update for the Generalist and Specialist, Divisions of Gastrointestinal and Liver Diseases, Albert Einstein College of Medicine and Montefiore Hospital and Medical Center, Riklis Auditorium, Albert Einstein College of Medicine, Bronx, NY, 29 April 1979.


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Effect of Cimetidine on Stimulated Gastric Secretion and Serum Gastrin in the Dog

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Birmingham, AL
and
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New York, NY

The histamine H-2 receptor antagonist cimetidine was given for 90 minutes to four fistula dogs during a steady dose 270-minute infusion of histamine (50 μg. base/kg.hr.), urecholine (80 μg./kg.hr.) or pentagastrin (1.5 μg./kg.hr). In each case there was gradual but marked (75-95%) inhibition of acid secretion with maximal effects after 60-90 minutes while pepsin secretion was also suppressed but to a lesser extent. These effects persisted for at least the 90 minutes after the end of cimetidine infusion. Serum gastrin was not significantly changed by cimetidine. Kinetics of effect of cimetidine were derived from step-dose responses to histamine (2-150 μg./kg.hr.), pentagastrin (0.1 to 10 μg.kg.hr.) and urecholine 20-160 μg./kg.hr.) which were made alone and with background infusions of cimetidine. Cimetidine acted competitively for acid output with histamine as the stimulus and noncompetitively for pentagastrin or urecholine. With histamine or pentagastrin pepsin was less inhibited than H^+ and in the case of urecholine, pepsin secretion was not inhibited by cimetidine.

Cimetidine is thus effective against all stimuli acting on the parietal cell to secrete acid, though the mechanism of this effect is unknown for the non-histamine stimuli. It is far less effective against agents which stimulate pepsin secretion. In the case of histamine, cimetidine blocks an action of histamine which, at high doses inhibits pepsin secretion.

From the Division of Gastroenterology, Department of Medicine, University of Alabama in Birmingham and the Birmingham Veterans Administration Hospital.

This work was supported by NIH Grants AMO9260, TIAMO5286, and 5-TO1-LM-00154, and the Medical Research Service of the Veterans Administration.

Cimetidine[1, 2] is the third in a series of antagonists of the H-2 receptor of histamine, the receptor through which histamine stimulates the gastric parietal cell to secrete electrolytes, the atrial pacemaker to speed cardiac rate and the rat uterus to contract. Studies with the two previous

compounds produced by Black and his colleagues[3] have shown that both burimamide and metiamide are also effective antagonists to histamine action on H^+ secretion [4-7] but that they block secretion of acid under other, less clearcut circumstances, such as the basal state in man [8-10] and secretion stimulated by gastrin or pentagastrin and by cholinergic stimuli, including urecholine and vagal stimulation. Furthermore, neither agent inhibited the stimulation of pepsin secretion.[5, 6, 8] In fact, when metiamide was given in combination with cholinergic stimuli in the same dogs,[6] pepsin secretion was augmented while acid secretion was inhibited.

Because atropine or vagotomy inhibit or reduce the action of noncholinergic stimuli, tentative hypotheses regarding possible interactions between receptors to histamine, gastrin and acetylcholine have been proposed.[7-11] No satisfactory model, however, has been proposed for the anomalous effect of the H-2 antagonist metiamide on pepsin secretion.[6] No study has reported the effect of cimetidine in fistula dogs. We here report the effects of cimetidine on gastric acid, chloride and pepsin in the gastric fistula dog stimulated by histamine, pentagastrin, urecholine, and vagally by insulin. Acid and electrolyte effects are very similar to those of the two previous antagonists[5, 6] while the pepsin secretion response to histamine is altered in such a way as to suggest that histamine both stimulates and inhibits pepsin release at low and at high doses respectively.

Methods

All experiment sets were done within a two-month period. For each set of experiments (control with the stimulus alone and then with cimetidine) four dogs (mean weight 25 kg. ± 1.6 SEM) with gastric cannula and Komarov esophagostomy were used. Each was in good health, had been trained in the conditions of the study and was studied in other experiments for at least one year before these studies were done.

The conditions of experimentation have been reported previously.[12] The dogs were fasted for 18 hours with water allowed and no experiment was started if there was basal secretion. In practice, basal secretion occurs not more than once in 30 studies. Drugs were given intravenously with a Harvard infusion pump and gastric juice collected by gravity drainage in consecutive 15-minute periods for up to 315 minutes. Aliquots were reserved for measurement of H^+ by titration to pH 7.0, Cl by coulombetric titration and pepsin by a hemoglobin digestion method using an autoanalyzer.[13] Output of each constituent was the product of concentration and 15-minute volume.

Stimuli were given in three ways: 1. by constant infusion at one dose for 4½ hours, with cimetidine given in the middle 1½ hours by I.V. infusion, and 2. in consecutive 45-minute incremental dose steps, using seven doses each of pentagastrin (0.1 to 10 μg./kg.hr.) and histamine (2-150 μg. base/kg.hr.) and five doses of urecholine (20-160 μg./kg.hr.). These dose responses were repeated against a background infusion of cimetidine given for a full duration of the stimulation. 3. Insulin 0.2 U./kg. was given in a single bolus I.V. and on another occasion at the start of a 4½-hour cimetidine infusion.

Serum gastrin levels were measured by radioimmunoassay[14] using a gastrin antibody (1296) kindly supplied by Dr. John Walsh.*

* Department of Medicine, U.C.L.A. School of Medicine, Los Angeles, CA.

TABLE I

MEAN (+ SEM) VOLUME AND CONCENTRATIONS OF H, CL AND PEPSIN AND THE RATIO OF PEPSIN:ACID CONCENTRATION (PU/H).

Min.	Vol. ml./15 min.		H^+ mEq./l.		Cl^- mEq./l.		Pepsin PU./ml.		Ratio PU/H^+	
	Control	Test	Control	Test	Control	Test	Control	Test	Control	Test
Histamine 50 μg./kg.hr.										
90	71 ±7.4	61 ±5.7	152 ±1.6	144 ±12.3	169 ±10	164 ±8	61 ±11	127 ±26	.41	.88
180	60 ±4.4	6* ±1.8	156 ±1.8	87* ±17	171 ±12	142* ±6	40 ±5	620* ±113	.25	7.1
270	44 ±3.5	15* ±1.1	152 ±4.2	125 ±11	171 ±3	161 ±6	47 ±15	489* ±96	.30	3.9
Pentagastrin 1.5 μg./kg.hr.										
90	67 ±8.5	54 ±8	150 ±3	143 ±8	170 ±2	168 ±4	397 ±100	526 ±145	2.6	3.7
180	48 ±3.5	9* ±1.6	150 ±2	119 ±17	170 ±2	155 ±9	476 ±98	1,804* ±485	3.2	15.7
270	39 ±1.6	21* ±5.3	151 ±2	136* ±1	171 ±1	155* ±4	280 ±31	1,703* ±430	1.8	13.1
Urecholine 80 μg./kg.hr.										
90	41 ±3.3	42 ±1.5	75 ±2.5	89 ±30	123 ±17	129 ±19	1,332 ±239	1,676 ±176	17.8	18.8
180	31 ±5.0	6* ±2.9	91 ±2.1	66* ±6.4	131 ±14	121 ±1.4	1,367 ±201	2,531* ±395	15.0	38.3
270	36 ±4.4	13* ±2.9	79 ±21	86 ±13.1	125 ±15	123 ±15.1	1,134 ±238	2,440* ±368	14.3	28.4
Insulin 0.2 U./kg.										
1st hr. 60	28 ±9.6	10 ±0.5	115 ±11.4	89 ±6.4	151 ±5.1	136 ±5.9	3,174 ±298	3,441 ±269	27.6	39
2nd hr. 120	23 ±5.4	11* ±1.9	145 ±2.7	90* ±18.6	160 ±2.3	139* ±7.4	2,760 ±420	4,613 ±892	19	51.2

Each value is the mean of four studies. In the insulin studies cimetidine 2 mg./kg.hr. was infused throughout the experiment but in the other studies from 90-180 minutes only. The stimulants were given for 270 minutes by continuous IV infusion.
*$P < .05$.

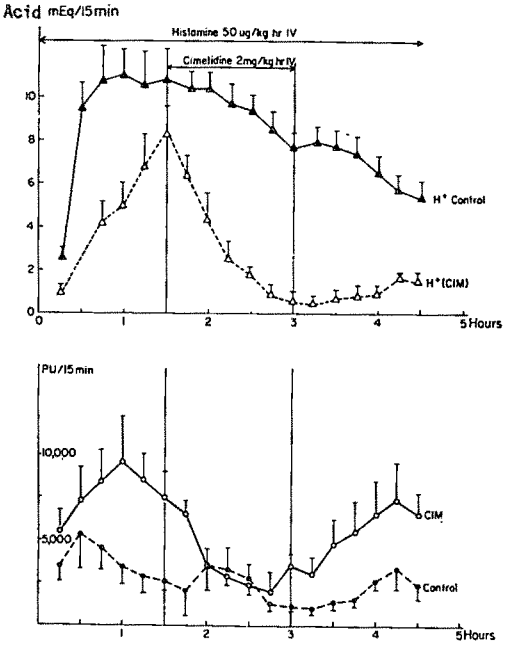


Fig. 1—Infusion of cimetidine in the middle 90 minutes of a 270-minute histamine infusion in four fistula dogs. Acid and pepsin outputs in controls and test. Means ± SEM, (n = 4).

Results

Single dose stimuli:—Doses of each of the major stimuli were chosen to give near maximal secretion responses for that stimulus and cimetidine at a dose which in preliminary testing gave greater than 80% inhibition was infused from 90-180 minutes beginning at about the time a steady state response to the stimulus had been obtained. These experiments were done to determine the speed of effect of the inhibitor, the rate of recovery from inhibition and the quantitative changes in gastric juice composition and to determine whether there was any effect on serum gastrin. The data are presented in two ways. The output of acid and pepsin are given in each of the first four figures for the stimulant infusion alone and for the stimulant with superadded cimetidine. The concentrations of acid, chloride and pepsin, and the ratios of pepsin:acid are given in Table I. In that table the mean values at the end of each 90-minute period are given, the first 90 minutes representing the infusion of stimulant alone, the second 90 minutes when cimetidine was infused and the third 90 minutes the end of the recovery period. The values in the untreated infusion (controls) at the same time periods are also given.

Exogenous stimuli:—Histamine:—The effect on acid secretion of cimetidine given in the middle 90 minutes of a 270-minute infusion of histamine was evident within the first 15 minutes and by the end of 90 miuntes of cimetidine, acid outpt was reduced to 0.6 mEq./15 min., i.e. by 93%, from control values (Fig. 1). The effect persisted with only slight recovery for the remaining 90 minutes of the study. Pepsin output was reduced by half during cimetidine infusion but subsequently recovered to precimetidine values. Though the studies were performed in the same dogs within one month of each other, the H^+ output during the control period was much lower in the test series and the pepsin higher. The effects of cimetidine, however, are clearly inhibitory to acid secretion and pepsin output.

A summary of volume and concentration changes in control and test is given in Table I. Those changes demonstrate a reduction in concentration to both H^+ and Cl and also a rise in pepsin, partly compensating for the 90% drop in volume during and after cimetidine. The lesser effect on pepsin is reflected in a four-fold increase in ratio pepsin:acid.

Pentagastrin:—Acid output was reduced progressively by cimetidine, reaching 50% inhibition at 30 minutes and a maximum of 85% inhibition at 90 minutes compared to the control values. Ninety minutes after the end of cimetidine infu-

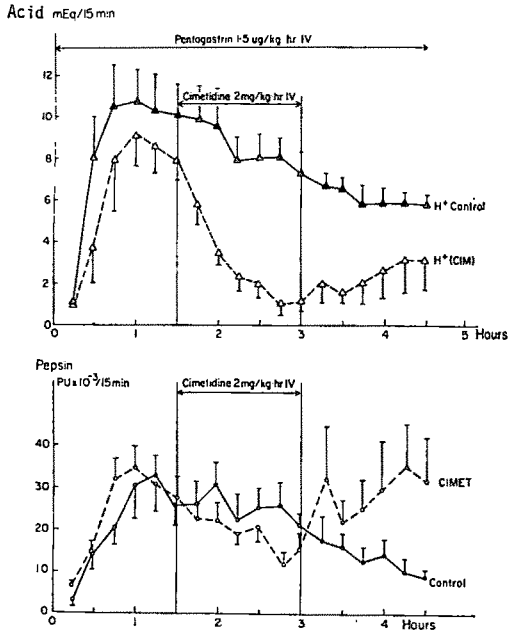


Fig. 2—Cimetidine infused during the middle 90 minutes of a 270-minute pentagastrin (1.5 ug./kg.hr.) infusion in four dogs, showing H^+ output, pepsin output, in test and control. Means ± SEM.

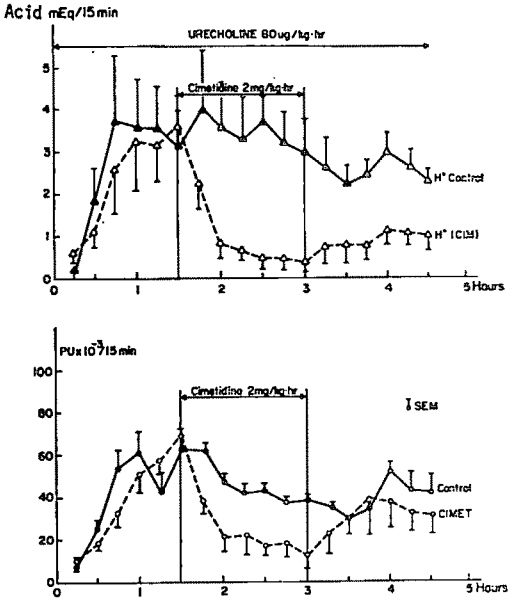


Fig. 3—Cimetidine infusion in the middle 90 minutes of a 270-minute urecholine infusion in four dogs showing H^+ and pepsin output in both studies. Means ± SEM.

sion, output was only half of that in the control studies (Fig. 2). Pepsin output was reduced by 50% at 75-90 minutes of cimetidine infusion and recovered after cimetidine to values equal to the precimetidine levels (Fig. 2). Although the trend was clearly down during cimetidine infusion, the values are not statistically lower than control.

Volume output was reduced over 80% (Table I) and the concentrations of acid and chloride reduced by 31 and 15 mEq./l. respectively. Pepsin concentration, however, rose three- to four-fold and the ratio pepsin:acid five-fold.

The effect of urecholine, a weaker stimulus of acid secretion, was reversed more rapidly by means of cimetidine. After 90 minutes of cimetidine, acid output was reduced 90%. Pepsin output was about one-third of control. After stopping cimetidine, acid output showed little recovery, while pepsin reached control levels in 30 minutes (Fig. 3). Serum gastrin was not affected by either urecholine or cimetidine (Table II). Ninety minutes after starting cimetidine, volume output was 80% reduced, while concentrations of acid and Cl were reduced 25 and 10 mEq./l. respectively. Pepsin concentrations were approximately twice control and pepsin:acid ratios were 2½ times that of control. The gastric juice composition remained about the same for the 90 minutes after stopping cimetidine.

Insulin (Fig. 4):—After insulin, 0.2 units/kg., by single bolus injection, gastric secretion continued for 4½ hours (Fig. 4) reaching peak values of acid about half of that with histamine and similar to the urecholine. Pepsin output at peak was half again as high as the urecholine stimulated peak outputs.

TABLE II

MEAN ± SE SERUM GASTRIN IN FOUR DOGS BEFORE AND DURING THE INFUSION OF THREE STIMULI

Time, min.	Histamine 50 μg./kg.hr.	Urecholine 80 μg./kg.hr.	Pentagastrin 1.5 μg./kg.hr.
0	9 ± .7	33 ± 13	16 ± 4
45	5.5 ± .6	45 ± 18	26 ± 3
90	6.3 ± 1.5	35 ± 13	27 ± 2
135	11 ± 4.9	33 ± 13	38 ± 9
180	8 ± .9	42 ± 15	38 ± 7
270	13 ± 2	46 ± 18	42 ± 8

	Insulin 0.2 units I.V. at time 0	
Time, min.	Control no cimetidine	+ cimetidine
0	35 ± 7	36 ± 3
30	48 ± 9	42 ± 9
60	40 ± 10	42 ± 11
90	53 ± 14	60 ± 7
120	–	64 ± 13
150	–	54 ± 8
180	53 ± 9	56 ± 7
270	46 ± 8	

In each case cimetidine was given by infusion during the period 90-180 minutes. In the insulin studies (0.2 U./kg. I. V. at time 0) one was done with an infusion of cimetidine for three hours and the other without cimetidine (see also Figs. 1-4) (n = 4 in each case).

Cimetidine reduced acid output by 75%. The early peak of pepsin output (30-90 min.) was eliminated but thereafter and until secretion stopped at three hours, was similar to control values (Fig. 4).

Volume output (Table I) was reduced in the first hour by two-thirds, while acid and Cl concentrations were reduced 26 and 15 mEq./l. respectively. Pepsin concentrations were increased by cimetidine over the high values seen with insulin alone. Pepsin:acid ratios were also increased especially in the second hour.

Serum gastrin:—Serum gastrin levels were measured during the infusion of each of the above stimuli before, during and after the superimposition of cimetidine. In no case did cimetidine cause any significant change in serum gastrin levels (Table II). There was a small increase from 16-42 pg./ml. during pentagastrin infusion (1.5 μg. or 1.5 × 10^6 pg./kg.hr.). This amount may be enough to be measured by the assay in the amounts indicated. There was no gastrin stimulation by histamine, urecholine or insulin alone, but insulin did stimulate gastrin to

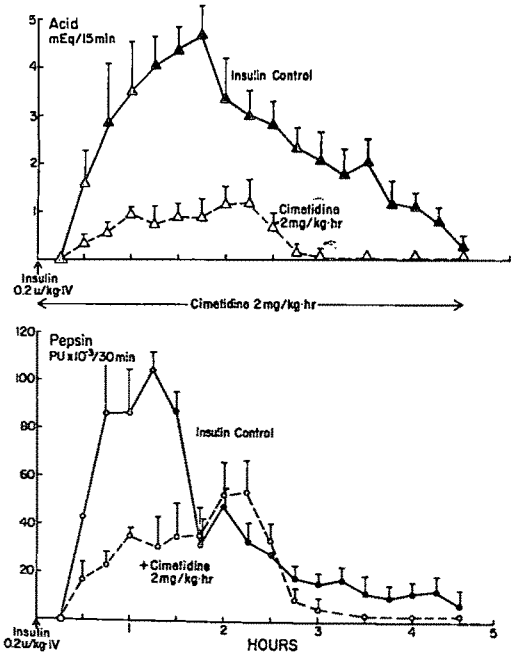


Fig. 4—H^+ and pepsin output and serum gastrin in three dogs given insulin, 0.2 u./kg. I. V. On another occasion in each, a 4½ hour cimetidine infusion 2 mg./kg.hr. was started at the time of insulin injection. Means ± SEM.

almost double fasting values during cimetidine (Table II).

Stimulus Dose Response Studies

Each of the three exogenous stimuli was tested against a background of cimetidine infused at a single rate throughout the dose response.

Histamine:—The typical acid dose response was shifted to the right by the 1 mg. cimetidine dose with a dose ratio shift at midpoint of 4.6 (i.e. the dose of histamine required to stimulate 10 mEq. HCl/30 min. was increased from 28 to 130 μg./kg.hr.) The larger doses of cimetidine shifted the curve even more to the right. Comparing the doses required to give 5 mEq./30 min., the dose shifts are 5.5 and 10.5 (12.5 to 70 and 130 μg. histamine/kg.hr. respectively) (Fig. 5). By

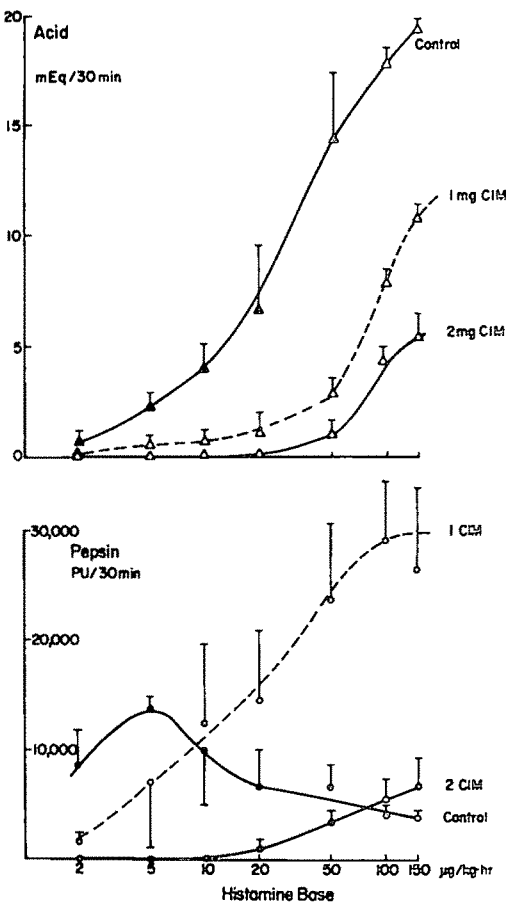


Fig. 5—Step-dose response of H^+ (top) and pepsin (bottom) output with incremental step-doses of histamine alone and at other times with background infusions of cimetidine 1 mg. and 2 mg./kg.hr. Mean ± SEM of four dogs, each point represents the output of the last 30 minutes of each 45-minute dose step.

moving the cimetidine curves to the left 5.5- and 10.5-fold respectively, they can be superimposed on the control curve, indicating that the effect of cimetidine is competitive.

Pepsin secretion was changed by cimetidine in two ways. First, the shape of the curve was changed from one with an early peak with dose reversal typical of histamine action in dogs, to a classical log-sigmoid curve (Fig. 5) and this curve was

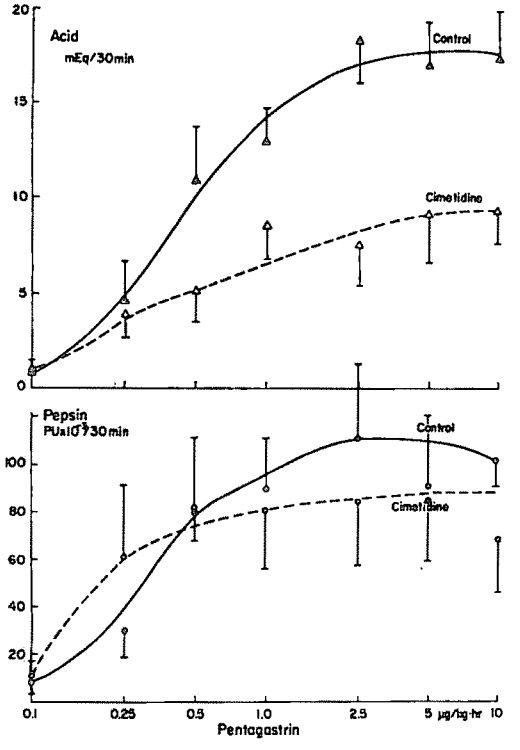


Fig. 6—Dose responsive H^+ and pepsin output with pentagastrin given alone and with a background of cimetidine 1 mg./kg.hr. Means ± SEM.

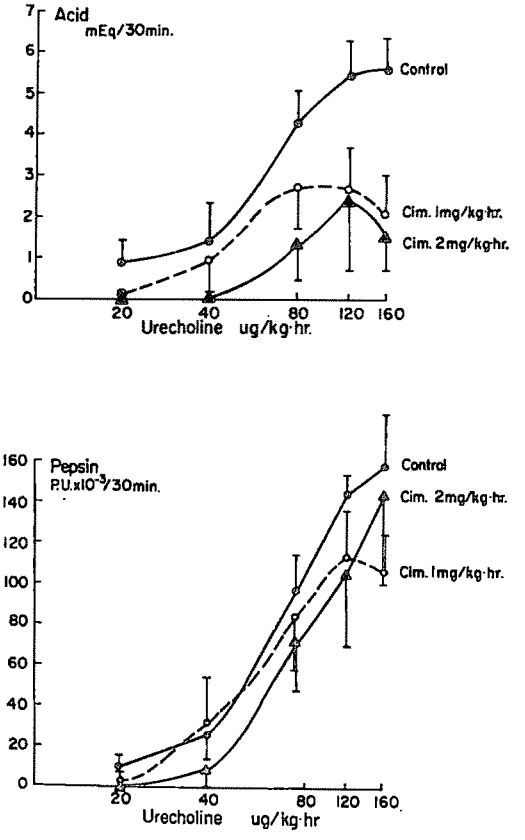


Fig. 7—Dose responsive output of H^+ and pepsin output with urecholine alone and with a background of cimetidine 1 mg./kg.hr. and 2 mg./kg.hr. Means ± SEM.

moved more to the right by the larger dose. Second, pepsin output in the histamine dose response was significantly greater with the lower dose of cimetidine than without (Fig. 5).

Pentagastrin:—Acid output was inhibited about 50% by cimetidine, 1 mg./kg.hr., with the observed and calculated maximal output about 9.4 mEq./30 min. compared to the control of 18 mEq./30 min. (Fig. 6). The dose ratio shift induced by cimetidine 1 mg./kg.hr. at 8 mEq./30 min. is 4.6 (0.26 vs. 1.60 μg./kg.hr.), a value similar to that for histamine. Pepsin output was reduced by about 20% at higher doses of pentagastrin. This was not significantly different from control at any dose.

Urecholine:—Acid output was markedly suppressed by a background of cimetidine, the 2 mg./kg.hr. dose having a greater effect than the 1 mg./kg.hr. In both cases peak secretion occurred at submaximal doses and the slope of the response curves appears to be noncompetitive.

Pepsin secretion, however, was only minimally affected by cimetidine (Fig. 7), with increases in concentration compensating for marked reduction in volume flow.

Comment

The bone marrow suppression by metiamide[15] attributed to the thiourea side-chain configuration, led to its withdrawal from clinical use and to the introduction

into physiologic and clinical testing of cimetidine, the pharmacology of which has been reported by Brimblecombe and his colleagues[1, 16] and by Burland, et al in man.[17] In secretory studies in man, cimetidine has been effective at about the same dose or blood concentrations as metiamide[2, 17, 18] and is also effective against meal[19] or caffeine stimulated secretion in man.[20] Our results show that in the dog, too, the effective dose for inhibition of H^+ secretion is about the same as for metiamide and that both are more potent than burimamide.[5] The effects of this compound, however, differ from metiamide[6] in not stimulating pepsin secretion when given with cholinergic stimuli.

The single dose stimulant experiments, with cimetidine given after a near-steady state had been reached, allow one to determine the speed with which cimetidine effects a change in composition and output of gastric juice. In all cases, cimetidine reduced secretion rather slowly with a half-time of about 30-40 minutes for acid output and a maximum effect at 75-90 minutes. The effect persisted quite long after discontinuing cimetidine indicating a slow rate of removal from the body. All four stimuli used—histamine and the nonhistamine stimuli pentagastrin, urecholine and vagal, i.e. exogenous and endogenous cholinergic, were sensitive to the inhibitor with reduction of volume and of H^+ and Cl^- concentration and persistence of effect for at least 90 minutes after a 90-minute infusion.

An inhibitor could in theory act at many different sites in the stimulus-to-secretion sequence, including diversion of stimulant, blocking or altering the receptor, interfering with the transducer mechanism, depressing cellular metabolism directly or indirectly, or inhibiting the release of the secretory product. From dose response studies it is sometimes possible to deduce from appropriate kinetic analyses that the action of an inhibitor is by competition with the stimulus for receptor sites. Such appears to be the case for the H-2 receptor antagonists including the cimetidine studied here, acting against histamine. Assuming furthermore that the action of cimetidine is confined to H-2 receptor antagonism, it is inescapable that histamine is critical to the stimulant actions on electrolyte secretion of cholinergic and of gastrin-like stimuli, since both are strongly inhibited by cimetidine and by metiamide. This evidence, if taken with data showing similar broad inhibitory effects of anticholinergic agents against noncholinergic stimuli, and the cooperative interaction between stimuli,[11] suggests that there is an essential interdependence between the receptors for the major stimuli of gastric acid and electrolyte secretion. The fact that the action against nonhistamine stimuli seems noncompetitive raises the question of an action other than receptor competition. There is not enough evidence from time of action, duration of effect or composition of gastric juice during inhibition to propose a site of action other than at receptor sites.

With respect to pepsin secretion, however, there is a different set of data to consider. Each of the H-2 antagonists behaves somewhat differently and the effects are different from those on electrolyte secretion. Burimamide reduced pepsin secretion in the dog with pentagastrin stimulation but had little effect on acid secretion at the doses which could be safely given,[5] whereas metiamide did not inhibit pepsin secretion with histamine or pentagastrin and, with exogenous or endogenous cholinergic stimulation, resulted in marked potentiation of pepsin secretion while acid secretion was inhibited with all stimuli.[6] This was also seen in the cat with electrical vagal stimulation (F. P. Brooks personal communication). Cimetidine does not have

this potentiation effect on pepsin secretion with urecholine, although it is equally potent against acid secretion. From the dose response studies, pepsin secretion was unaffected but the single dose urecholine or the insulin hypoglycemia stimulation of pepsin were suppressed by cimetidine at the same dose. We are not sure why this difference occurred.

The effect of cimetidine on dose-responsive pepsin secretion with histamine stimulation suggests the possibility that the antagonist may block inhibitory effects of histamine on pepsin secretion in the dog. Thus the response to histamine shows a biphasic curve with stimulation at low doses and inhibition with higher doses (Fig. 5). With cimetidine (1 mg./kg.) the curve changes to one which shows stimulation up to the higher doses and reversal of effect at 150 μg./kg.hr. The bigger dose of cimetidine shifts this curve more to the right. One interpretation for these changes and which we favor, is that histamine has both inhibitory and stimulant effects and that at lower doses the latter predominate and at higher doses the former, giving a biphasic curve. There is no evidence thus far that any H-1 receptors are involved.

The different effects of the three H-2 antagonists show that pepsin stimulation and inhibition by histamine cannot be simply classified. Stimulation by metiamide and not the others suggests that the thiourea sidechain may be important in this action, since neither 4-methylhistamine[18] nor 4-methyl imidazole (unpublished observations) has unusual effects on pepsin secretion.

Cimetidine has been studied in man where it is a potent inhibitor of acid secretion stimulated by various stimuli[19-22] It has no effect on serum gastrin as shown here and in man,[22] possibly except for a small increase in food-stimulated gastrin release when antral acidification is prevented.[19] The evidence does not support a role for histamine in the release of gastrin.

Further data will be needed before it is possible to propose reasonable mechanisms for the action of the H-2 histamine receptor antagonists against nonhistamine stimuli and for the unexpected stimulant action of metiamide[6] on pepsin secretion in dogs and cats when combined with cholinergic stimuli.

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Distinguishing Between Malignant and Cirrhotic Ascites by Computerized Step-wise Discriminant Functional Analysis of Its Biochemistry

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This study was designed to evaluate the ability of a specifically programmed computer to select those biochemical substances most capable of distinguishing "cirrhotic ascites" from "malignant ascites". After simultaneously performing selected biochemical and electrophoretic studies on fresh unstored serum and ascites of 23 patients with documented cirrhosis and 18 patients with proven malignancies, computerized step-wise discriminant analysis of the multiple input revealed that the serum-to-ascites LDH ratio was able to distinguish "cirrhotic ascites" from "malignant ascites" with greater than 86% accuracy. Assignment to proper groups was increased to 89% with the addition of the ratio to serum total protein-to-ascites total protein. The predictive value of a positive result was 100%; specificity was 100%; the predictive value of a negative result was 85%. This type of computer analysis also permits incorporation of both additional cases and new substances thus increasing predictability and reducing type II statistical errors.

The ability to accurately distinguish between "cirrhotic" and "malignant" ascites by readily available biochemical technics would frequently avoid performing many expensive time consuming diagnostic studies on patients presenting with ascites of unknown etiology. While cytologic study of peritoneal effusions might be the single most accurate method of distinguishing "malignant" from "cirrhotic" ascites, this technic requires the expertise of a highly trained cytologist because of the frequent presence of morphologically confusing mesothelial cells exfoliated from the peritoneum.[1, 2]

The purpose of this study was to ascertain whether, after performing multiple simultaneous biochemical analyses on specimens of fresh serum and ascites from individual patients with proven cirrhosis or documented malignancies, computer technics could be employed to accomplish the following: 1. Find significant and reproducible differences in the absolute value of one or more biochemical substances in the serum of patients with "cirrhotic ascites" versus their values in the serum of patients

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with "carcinomatous ascites". 2. Find significant differences in the absolute levels of one or more biochemical substances in the ascitic fluid of cirrhotics from their absolute levels in "malignant ascites". 3. Find significant differences between the serum-to-ascites fluid ratio of one or more biochemical substances in patients with "cirrhotic ascites" versus this ratio in patients with "malignant ascites".

Selection of Patients

The selection criteria required for patients to be included in this study necessitated the following:

1. The presence of readily accessible ascites of unknown etiology.

2. The absence of any therapy for this ascites prior to removal of the samples employed for this study.

3. The diagnosis of cirrhosis, if initially made by liver biopsy, was required to be confirmed by necropsy in order to exclude the presence of a coexisting carcinoma as a possible contributing cause of ascites.

4. The diagnosis of carcinoma, if initially made by tissue removed at laparotomy or other biopsy procedure, was required to be confirmed by necropsy in order to exclude concomitant cirrhosis as a contributing factor to the presence of ascites.

5. All patients included in this study died during the hospitalization period in which their ascites was analyzed. The period between this analysis and the patient's demise averaged 42 days.

The use of such rigid patient selection criteria excluded 13 patients from the original group. Absolute certainty of diagnosis plus elimination of the possible influence of prior therapy of the ascites, however, was felt to be essential for the integrity of this study.

Applying these criteria to the original study group of 54 patients over a two-year period permitted inclusion of the 41 patients comprising the substance of this report. Of this group, 23 suffered from cirrhosis with ascites while in 18 patients, ascites was caused by carcinomas whose primary sites varied.

Technics

After obtaining an individual's informed consent, 30 ml. of ascitic fluid and 30 ml. of blood were drawn from each patient via separate 30 ml. syringes and 20 gauge needles within five minutes of each other. All chemical and electrophoretic analyses performed on the serum and ascites from each individual patient were begun simultaneously at room temperature within one hour of receipt of specimens and following centrifugation at 2,500 r.p.m., for five minutes. Any specimen of serum or ascites from an individual patient which was hemolyzed or grossly bloody was excluded from this study. In order to avoid storage related reduction of certain biochemical substances, these simultaneously performed studies on individual specimens of serum and ascites were begun less than one hour after their removal from each individual patient and completed within six hours with the exception of immunoglobulin electrophoresis. All biochemical determinations were carried out at room temperature. Serum and ascitic fluid specimens thus obtained were simultaneously analyzed for calcium, inorganic phosphorus, glucose, urea, uric acid, cholesterol, total protein, albumin, total bilirubin, alkaline phosphatase, SGOT and LDH* employing the Technicon SMA 12/60 Multiple Analyzer. Both serum and ascitic fluid protein electrophoresis were simultaneously carried out on the Titan Zip Zone plates

* LDH—Total lactic dehydrogenase activity.

2.3/8″ × 3″ in size. These plates were cellulose acetate with a mylar backing. The chamber was prepared by placing about 50 cc. of the buffer into each of the outer components. Samples were then inoculated onto the Titan III plates. Disposable paper wick, one for each compartment, was wet in the buffer and draped over the support bridge making certain of a good buffer contact. The inoculated Titan III strip was then placed with the cellulose acetate side down, being certain of contact with the wicks via glass slides placed on the plate for weight. The chamber was closed and electrophoresis run at 180 volts for 15 minutes. The protein bands were then stained with Ponceau Red S (Titan) for five minutes. The plates were then destained in three successive washes at 5% acetic acid: methanol (1:3) for four minutes. The plate was then air dried for one minute and placed on a Salton Hot Plate until acetate was clear and hard. The plate was then quantitated in a photovolt desitometer (see LHD Isoenzyme procedure).

Immunogobulins were determined using immunoglobulin plates obtained from Kallestad Laboratories, Minneapolis, MN, according to the manufacturer's instructions. Inoculation was made at 3:00 p.m. and read at 9:00 a.m. on the following morning. The wells were filled via a small capillary tube until the serum or fluid was raised about the well with a slight roundness. Each run was accompanied by three standards. All plates were incubated overnight in a horizontal position at room temperature. The following morning all percipitin rings were read with a Finesdale Comparator #122 in 0.1 mm. divisions in front of a Lab-Tek Contrast Lite. A graph was plotted on semilog graph paper with the immunoglobulin levels on the Y-axis and the diameter of the rings in 0.1 mm. on the X-axis. A straight line was drawn through these standards and the serum or

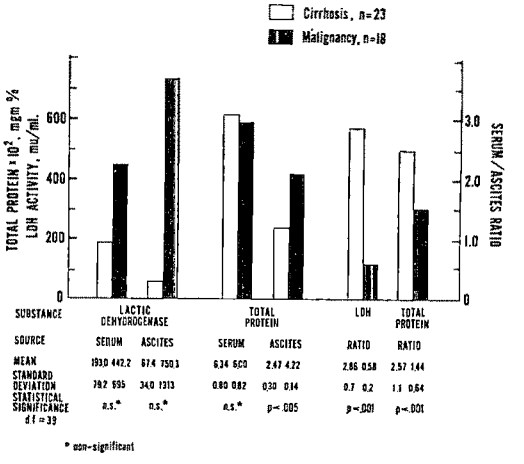


Fig. 1—LDH activity and total protein values in patients with cirrhotic and malignant ascites.

ascitic fluid levels calculated on this standard curve. Results were reported in mg.%.

LDH isoenzyme separation was performed via electrophoresis employing Electra HR Buffer diluted to 100 cc. at 215 volts for 15 minutes on 1″ × 3″ Titan III cellulose acetate plates. Power was supplied by a Buchler D.C. supply (model 3-1008). LDH isoenzymes were localized by means of the Titan LDH Isoenzyme Kit according to the manufacturer's instructions. A photovolt densitometer (Densicord model 452AO and filter of 750 mm.) was used to quantitate the LDH isoenzyme fractions.

Each of the biochemical substances analyzed in the freshly obtained serum and ascites of every individual patient and their serum-to-ascites ratios were introduced into a computer programmed for stepwise discriminant functional analysis in order to determine the variable or variables most accurately able to distinguish "cirrhotic ascites" from "malignant ascites". As a result of the computer derived information, our attention was focused upon LDH and total protein of serum and ascites in separating these two patient populations.

Results

Figure 1 depicts the mean serum and mean fluid LDH values with their corresponding standard deviations in patients with cirrhosis and patients with malignancies. For cirrhotics, the mean serum LDH was 193 μ./ml. (S.D. 79.2) and the mean ascitic fluid was 67 μ./ml. (S.D. 34). In those patients with malignancies, the mean serum LDH was 442 μ./ml. (S.D. 695) and mean ascites LDH was 750 μ./ml. (S.D. 1313). Because, however, of the extreme variations of LDH activity of both serum and ascitic fluid within patients of each class studied, i.e. the large standard deviations, the measure of central tendency alone was found to be of little diagnostic significance. Therefore, from our original study we must conclude that *solely* on the basis of mean serum LDH activity or mean ascitic fluid LDH activity, it is extremely difficult to distinguish *statistically* between ascites caused by cirrhosis and ascites caused by malignant disorders.

In an attempt to ascertain whether the serum and fluid LDH concentrations could, in any manner, be employed to distinguish cirrhotic from malignant ascites the *ratio* of *the mean serum value of LDH to its corresponding mean fluid LDH value* for each patient, regardless of class, was calculated. The arguments to support this operation are as follows: 1. It was observed from the raw data that in almost every case in the malignant group serum LDH activity was accompanied by a higher ascitic fluid LDH activity, whereas in each cirrhotic patient serum LDH activity was accompanied by a lower fluid LDH activity. The *ratio* of serum-to-fluid LDH activity remains relatively constant, and this constancy is reflected by a small variance. 2. When dealing with absolute values, one of the variables which must ultimately be controlled is the normal value for a particular laboratory. When, however, ratios are used this error is partially eradicated. It is most significant when the absolute values of LDH are small. The results of these serum-to-ascites ratios proved to be of great value in distinguishing "cirrhotic" from "malignant" ascites.

In Figure 1 is also indicated the mean of the serum-to-ascites ratios of LDH and total protein for each class of patients. This was determined by establishing the serum-ascites-ratio of LDH and serum-to-ascites ratio of total protein for each patient and then calculating the mean and standard deviation of those values for the entire group of patients with cirrhosis and the total group with malignancies. It can be readily observed from this table that the mean serum-to-ascites LDH ratios and mean serum-to-ascites total protein ratios of the cirrhotic and malignant groups are statistically significantly different. Figure 2 illustrates the distribution of serum-to-ascites LDH ratios for each of the 23 patients comprising the cirrhotic group and for each of the 18 patients comprising the carcinoma group.

Comments

Each of the biochemical substances analyzed in the freshly obtained serum and ascites of every individual patient and their individual serum-to-ascites ratios were introduced into a computer programmed for step-wise discriminant functional analysis in order to determine the variables most accurately able to distinguish between cirrhotic patients with ascites vs. patients with carcinoma plus ascites. Based upon the original data obtained from the 23 cirrhotic patients and 18 patients with malignancies who met the criteria for inclusion in this study, 86.6% of the patients could be correctly assigned to their proper groups solely on the basis of the serum-to-ascites LDH ratios. This assignment to proper groups was increased to 89% by the inclusion of

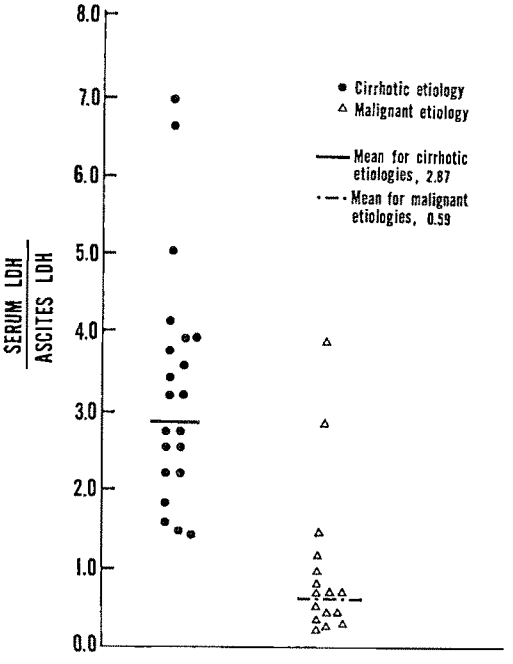


Fig. 2—Distribution of serum LDH-to-ascites LDH ratios for patients with cirrhosis and patients with malignancies.

the ratios of serum total protein to ascites total protein concentrations. The computer analysis method is advantageous in that each time a new patient with ascites is encountered, data may be collected and incorporated into the program in order to increase predictability. Moreover, when an interest in new variables develops, i.e. C.E.A. or alpha-fetoprotein, the value of these data may be compared to that of the original data and appropriate additions or deletions made. Such systematic analysis assists the clinician in evaluating the etiology of ascites in a given patient.

After the step-wise regression analysis on the multivariable matrix of inputs established that the serum-to-ascites LDH ratio was the single most statistically significant determination whereby cirrhotic peritoneal effusions could be distinguished from carcinomatous ascites, a carefully selected survey of other studies of LDH with respect to the faculty was carried out.

Evidence to suggest that elevated serum LDH levels herald the presence of malignancy is readily found in the literature.[3-5] Also, it is generally agreed that patients with cirrhosis do not often have markedly elevated serum LDH activity. This enzyme has been considered to be an insensitive index of chronic hepatic parenchymal damage such as is present in cirrhosis.[6-9]

Wroblewski logically extended the assay of LDH to various effusions and found that the elevated effusion LDH suggested its malignant origin.[10-12] Wroblewski considered that peritoneal effusions are cultures *in vivo* which bathe mesenchymal or malignant cells. If malignant cells in tissue culture contribute LDH to the bathing medium, it was to be expected that effusions either containing malignant cells or bathing malignant tissue would be enriched with this enzyme derived from the growing malignant cells. Since LDH is a globulin and serous effusion globulins come into equilibrium with the serum globulins slowly, the LDH activity of the effusion tends to accumulate in the relatively loculated effusion and gradually reaches levels greater than that of the serum of the same individual. Experimentally, the increase in LDH activity in tissue culture media appeared to be related to cellular growth rate rather than to characteristics of the type of cell. It has been speculated that the accumulation of LDH activity in the fluid bathing malignant cells resulted from the diffusion of LDH through the cell wall or escape of this enzyme into the media at the time of cell division. Illustrating this point, an increase in the total LDH activity has been found in cerebral cyst fluid from malignant cerebral tumors, but not in the cyst fluid from benign intracranial tumors.[13]

Studies by other authors of the LDH in pleural effusions[14, 15] and peritoneal ef-

	NUMBER WITH RATIO <1	NUMBER WITH RATIO >1	TOTALS
NUMBER MALIGNANCY	14	4	18
NUMBER CIRRHOTIC	0	23	23
TOTALS	14	27	41

Sensitivity = 80% (78%)
Specificity = 100%
Predictive Value of a Positive Result = 100%
Predictive Value of a Negative Result = 85%
Efficiency = 90%

Fig. 3—Sensitivity, specificity, predictive value and efficiency of $\frac{\text{LDH ascites}}{\text{LDH serum}}$.

fusions[16, 17] further suggested that this enzyme might be utilized to distinguish malignant from benign effusions. Two recent studies of the characteristics of various types of pleural effusions found the absolute level of pleural fluid LDH and the ratio of pleural fluid-to-serum LDH to be of value in differentiating those effusions which were benign (transudates) from those which were of inflammatory or malignant origin (exudates).[14, 15]

Other researchers, however, strongly denied the value of employing LDH as an aid in distinguishing benign from malignant effusions.[18-20]

In order to ascertain the reason for such opposing viewpoints, a careful review of the methodology utilized by authors with opposing views was performed. It readily became apparent that the earlier workers employed widely varying methods of storing ascites prior to its analysis because little information with respect to the lability of LDH isoenzymes at varying temperatures was then available. Zondag[21] first reported total loss of activity in the slower moving LDH isoenzymes at −20° C. In human serum, complete inactivation of LDH-4 and LDH-5 kept at −20° C occurred after two weeks. A pilot study carried out in this laboratory revealed that freezing and re-thawing serum and ascitic fluid led to substantial reduction of their total LDH activity. This loss of LDH activity was found to be relatively greater in ascites than in serum and approached 50% loss of its original activity after storage at −20° C for four months. The failure to employ uniform methods of storage of serum and ascites specimens was not emphasized in the earlier studies nor was the value of the serum-to-ascites LDH ratio emphasized. These factors could readily explain the lack of unanimity of opinion regarding the clinical value of serum-to-ascites LDH ratio in distinguishing "cirrhotic" from "malignant ascites."

Conclusion

In an attempt to distinguish "cirrhotic" from "malignant" ascites, a computerized step-wise regression analysis of the input matrix of various biochemical substances was studied in individual specimens of fresh serum and ascites. The serum-to-ascites ratio of these substances was also determined in these patients, i.e. 23 cirrhotic patients and 18 patients with carcinomas arising from varying primary sites was carried out. This step-wise discriminant functional analysis revealed that by employing serum-to-ascites LDH ratios as the sole criterion, greater than 86.6% of the patients were assigned to their proper groups. This predictability of assignment to proper groups was increased to 89% when the ratio of serum total protein-to-ascites total protein was added as a discriminating factor. The predictive value of a positive result was 100%. The predictive value of a negative result was 85%. The specificity was 100% (Fig. 3). This study suggests that the absolute levels of LDH found in serum or ascites of patients with

cirrhosis versus patients with malignancies could not be relied upon to distinguish between cirrhotic and malignant peritoneal effusions. When, however, the serum-to-ascites LDH ratio was found to be less than unity, this was strongly suspicious of a malignant etiology of the ascites. On the contrary, a serum-to-ascites LDH ratio greater than unity was good reason to suspect that the ascites was caused by cirrhosis. If one is cautious and assumes that all serum-to-ascites LDH ratios less than unity are due to causes other than cirrhosis, there were no false positives in this patient group.

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The Secretin Story

A Saga in Clinical Medicine and Gastrointestinal Physiology

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In 1902, Bayliss and Starling discovered secretin, a chemical messenger initiating a physiologic response at some distance from its origin; an active agent which they gave the term "hormone".[1] This concept resulted in a schism between East and West antedating the political revolution and like it still unresolved, i.e. only crude models exist attempting to integrate nervous and hormonal regulations of physiologic activity. These might be summarized as viewing the complex corporeal cybernetic system to include first a *course regulator,* the hormones which turn on or off the physiologic events and second the fine *adjustment* or nervous regulation which tunes in the speed of activity by manipulating energy flow, milieu of reaction and blood supply.

It took the customary 25 years before this basic science bore clinical application in the use of secretin to study pancreatic secretion in health and disease, which investigations yielded valuable and relevant data in the following areas: 1. the diagnosis of pancreatic disease; 2. the mechanisms of pancreatic secretion; 3. the estimation of pancreatic secretory capacity; 4. the pathogenesis of pancreatic inflammation; 5. the pancreatic contribution or involvement in various gastrointestinal disorders and 6. the evolution of the APUD concept.

Diagnosis of Pancreatic Disease and Estimation of Pancreatic Secretory Capacity

The early investigations of Lagerlöf[2] and Dreiling,[3] established that with precise placement of a duodenal tube under fluoroscopic control and with continuous suction, quantitative collection of duodenal contents uncontaminated by gastric juice was possible. Pancreatic responses to stimulation by a bolus I.V. injection of secretin, thus, could be studied in patients with and without pancreatic disease. In the normal subject, such stimulation resulted in a profuse flow of a juice high in bicarbonate content and low in enzyme protein (Fig. 1). The pancreatic response thus could be characterized by rate of flow, bicarbonate concentration, rate of bicarbonate secretion, enzyme concentration, and rate of enzyme secretion. Both Lagerlöf[2] and Dreiling[3-5] evolved identical protocols on the basis of statistical studies in patients without pancreatic disease, i.e.: 1. the use of a standard per kilogram bolus stimulus of secretin, 1 clin. unit; 2. a 90-minute collection period in 10- to 20-minute specimens; 3. the choice of rate of flow, maximum bicarbonate concentration, and rate of enzyme secretion as the discriminate parameters and 4. the conversion of flow and enzyme data to a per kilogram basis.

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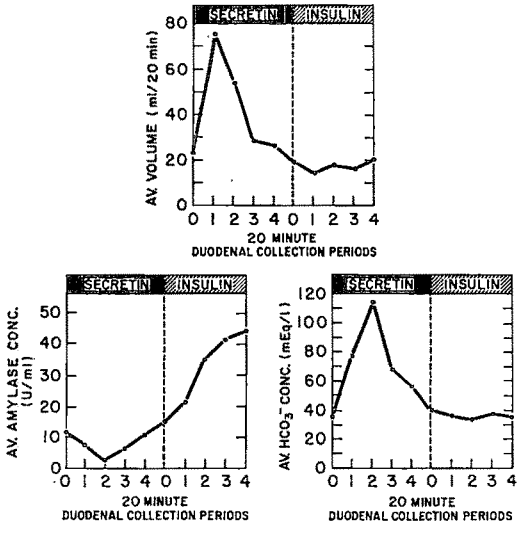


Fig. 1—Flow, bicarbonate and enzyme (amylase) responses of the human pancreas to stimulation by intravenous secretin and intravenous insulin (equivalent of CCK-PZ).

Both investigators,[2, 4, 5] from studies of large series of control patients, established the normal ranges for these parameters as follows: 1. rate of flow—2.0-4.0 ml./kg.; 2. maximum bicarbonate concentration—90-130 mEq./l.; 3. rate of enzyme secretion (amylase)—6.0-18.0 U./kg.

In the initial studies, investigators were intent upon disclosing abnormal pancreatic secretion, i.e. deficiency states, so that only the lower limits of normal were considered in interpreting the data. Based upon the findings in patients with pancreatic disease, five patterns of response were described by Dreiling:[6, 7] 1. total deficiency; 2. qualitative deficiency; 3. quantitative deficiency; 4. isolated enzyme deficiency; 5. discordant secretion.

The *total deficiency response* was characterized by low flow, low maximum bicarbonate concentration and low enzyme output. It implied either extensive destruction of secreting parenchyma (end stage chronic pancreatitis) and/or complete pancreatic duct obstruction (huge cancers of the head of the pancreas), differentiation between which required the development and application of cytologic studies of the duodenal drainages obtained. The *qualitative deficiency response*[7] disclosed normal flow, low maximum bicarbonate concentration and normal enzyme secretion. This secretion was observed in patients with pancreatic inflammation (Table I). This inability to secrete a high bicarbonate juice, though not initially understood, was characteristic of chronic pancreatitis and is illustrated in Figure 2, in which bicarbonate concentration is plotted against rate of flow in patients without pancreatic disease and patients with chronic pancreatitis. In both, with increasing flow, there is an increase in bicarbonate content but, at the same rate of flow, the patients with inflammation always secrete a juice of lower bicarbonate content than normal (Fig. 2). The *quantitative deficiency pattern*[6] was one in which the flow was markedly reduced but the bicarbonate and enzyme responses were normal (Table I), the degree of deficiency depending upon the site and severity of pancreatic duct obstruction. It was obvious from the early results that quantitative deficiency was diagnostic of pancreatic tumors in the head and body of the gland but that tumors of the pancreatic tail neither obstructed nor replaced sufficient parenchyma to produce this pattern of secretion. The remaining two patterns of secretion, *isolated enzyme deficiency* and *discordant secretion*, were recognized in the early studies which perforce included patients with various gastrointestinal disorders. Isolated enzyme deficiency (Table I) was characterized by normal flow, normal bicarbonate and low enzyme secretion. It was observed in patients with severe nonmalignant malnutrition. Discordant secretion was discordant because it combined features of hypo- and hypersecretion, i.e. extremely high flow with inappropriately low bicarbonate and normal enzyme secretion (Table I). This pattern of secretion

TABLE I

FLOW, BICARBONATE AND ENZYME DATA OBSERVED IN PATIENTS WITH PANCREATIC DISEASE

	Pattern	Flow	Maximum HCO_3 concentration	Amylase secretion
	Total insufficiency	↓	↓	↓
Chronic pancreatitis	Qualitative insufficiency	N	↓	N
Pancreatic cancer	Quantitative insufficiency	↓	N	N
Malnutrition*	Isolated enzyme deficiency	N	N	↓
Hypersecretion†	Discordant secretion	↑	N	N

* Sprue, ulcerative colitis and regional enteritis.

† Hemochromatosis, Zollinger-Ellison syndrome and various cirrhoses.

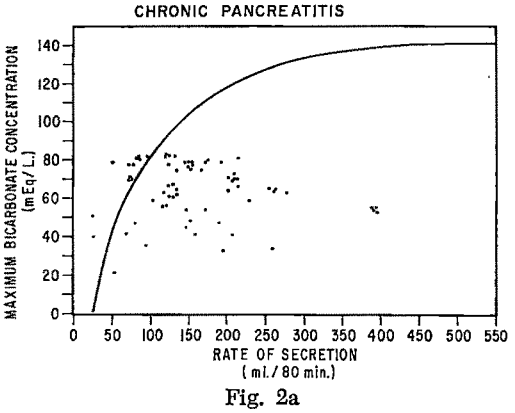


Fig. 2a

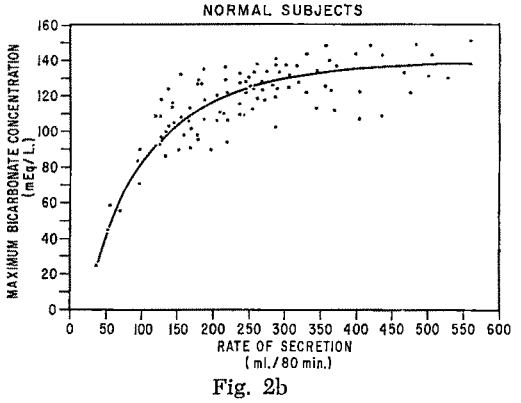


Fig. 2b

Figs. 2a and 2b—Flow vs. bicarbonate data in patients with and without pancreatic inflammation following secretin stimulation.

was inexplicable at the time and seen primarily in patients with hemachromatosis. The full significance of these patterns of secretion required elucidation of the mechanisms of pancreatic secretion, the pathogenesis of pancreatic inflammation and an understanding of the regenerative capacity of the gland in response to injury.

The ability of pancreatic secretory data to disclose pancreatic dysfunction and disease having been demonstrated, attention of the pancreatic physiologist and clinical investigator was directed towards additions and modifications of protocol which might add to the clinical usefulness and accuracy of the data.



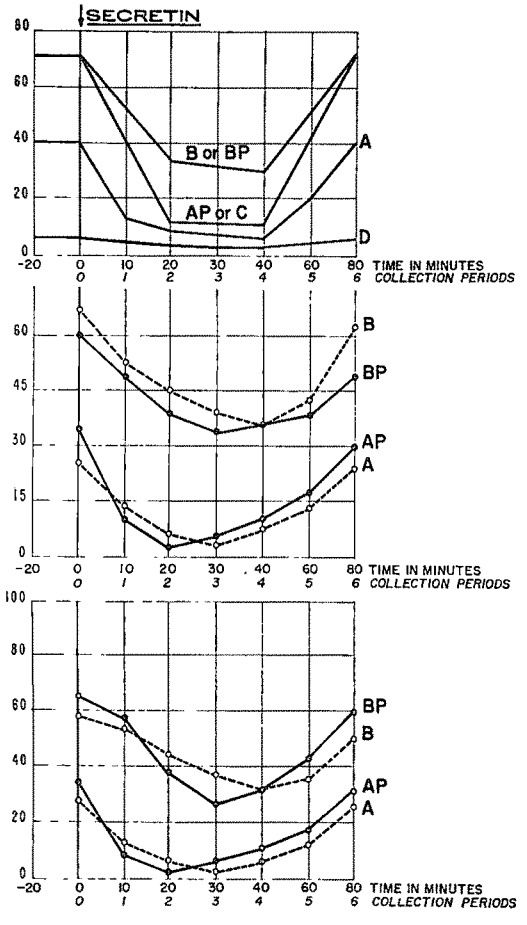


Fig. 3—Biliary pigment response curves during the secretin test. Icterus index is plotted against collection time.

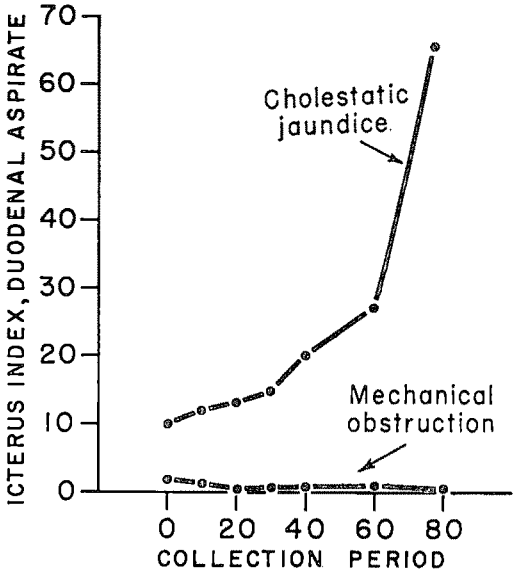


Fig. 4—Biliary pigment response curves following secretin. Cholestatic vs. mechanical "obstructive" jaundice.

The clinically significant *additions* to the secretin test procedure include: 1. study of the biliary contributions to the duodenum following secretin; 2. cytology; 3. study of other parameters, e.g. C.E.A., pancreatic specific RNase, secretory immunoglobulins, etc.

Determination of bile concentrations in duodenal drainage following secretin furnishes information concerning the patency of the extrahepatic biliary tract, the state of function of the gallbladder and sometimes evidence of intrahepatic disease, information of value in interpreting pancreatic function in patients with jaundice.[8] The patterns of secretion observed depend upon secretin stimulation of fluid and electrolyte from liver ductules; the flow of bile into the major hepatic duct; the accumulation of the biliary secretion in a gallbladder reservoir and the dilution of this secretin-induced biliary flow by pancreatic juice in the duodenum. The latter condition implies that biliary response patterns to secretin cannot be interpreted in patients with markedly depressed pancreatic flows (less than 1.0 ml./kg.). The biliary response patterns (Fig. 3) are:

Type A:—Dilution and/or disappearance of bile during the periods of maximum pancreatic flow. This pattern is characteristic of a reservoir signifying normal gallbladder function; when observed following cholecystectomy it indicates marked common duct dilatation with ball valve obstruction (AP).

Type B:—All collections throughout the secretin test remain heavily bile tinged.

TABLE II

SCHEMA COMBINING PANCREATIC AND BILIARY RESPONSES TO SECRETIN IN DETERMINATION OF LESION SITE IN PATIENTS WITH "OBSTRUCTIVE JAUNDICE"

Pancreatic response	Biliary pigment response	Lesion site
Obstruction	Obstruction	Head of pancreas
Normal	Obstruction	Extrahepatic bile ducts
Normal	Normal	Intrahepatic

This pattern indicates the absence of a biliary reservoir as seen in patients with nonfunctioning gallbladders (B) and following cholecystectomy (BP).

Type C:—Bile is absent throughout the secretin test and cannot be elicited in duodenal drainage by cholecystokinetic agents ($MgSO_4$ or CCK-PZ). This pattern confirms mechanical obstructive jaundice. A subset of this pattern is the observation of absence of biliary pigment in duodenal drainage before secretin, its appearance in good concentration following secretin and the failure of cholecystokinetics to elicit recurrence of bile in the duodenal collections following secretin in jaundiced patients. This "wash-out" phenomenon implies patent extrahepatic ducts and indicates intrahepatic block or cholestatic jaundice (Fig. 4).

The combination of pancreatic and biliary pigment responses can be of assistance in the differential diagnosis of obstructive jaundice by indicating the site of obstruction (Table II). The possibilities are three: 1. obstruction to both pancreatic and biliary flow would indicate a lesion in the head of the pancreas, i.e. tumor; 2. obstruction to biliary flow with normal pancreatic secretion would indicate common bile duct pathology, be it stricture, stone, or tumor and 3. normal pancreatic flow and biliary flow following secretin in a clinically "obstructed" jaundiced patient indicates intrahepatic disease.

Tiscornia[9] has extended this type of study by a modification of the standard secretin test protocol as follows: 1. After initial intubation, the duodenum is infused for 5-10 minutes with 20 gm. of sorbitol (70 ml.) which incites a flow of pancreatic juice, bile and contraction of the gallbladder by release of CCK-PZ activity from duodenal mucosa. 2. Duodenal drainage collection is started following an I.V. injection of BSP. Just 1.0 ml. of indicator is used if BSP appearance time (25 min. or less—normal) is to be determined. I.V. BSP (5 mg./kg.) is required for liver function evaluation. During the 30 minutes in which BSP is monitored in the duodenal collections, determination of pancreatic ferments in the drainage gives an estimate of the enzyme secretory function in terms of peak enzyme concentration and output. 3. Finally a standard secretin test is performed.

Such a protocol, obviously, permits evaluation at the same time of hepatic function, patency of the biliary tract and pancreatic function.

Cytologic study of duodenal contents following secretin has added to the diagnostic value of the data especially in disclosing lesions of the tail and uncinate process of the pancreas, in the diagnosis of cancer of the biliary tract and in revealing malignancy in end stage chronic pancreatitis with total deficiency secretory patterns. While the percentage accuracy depends not only upon the preservation of tumor cells by collection of specimens under refrigeration and careful preparation

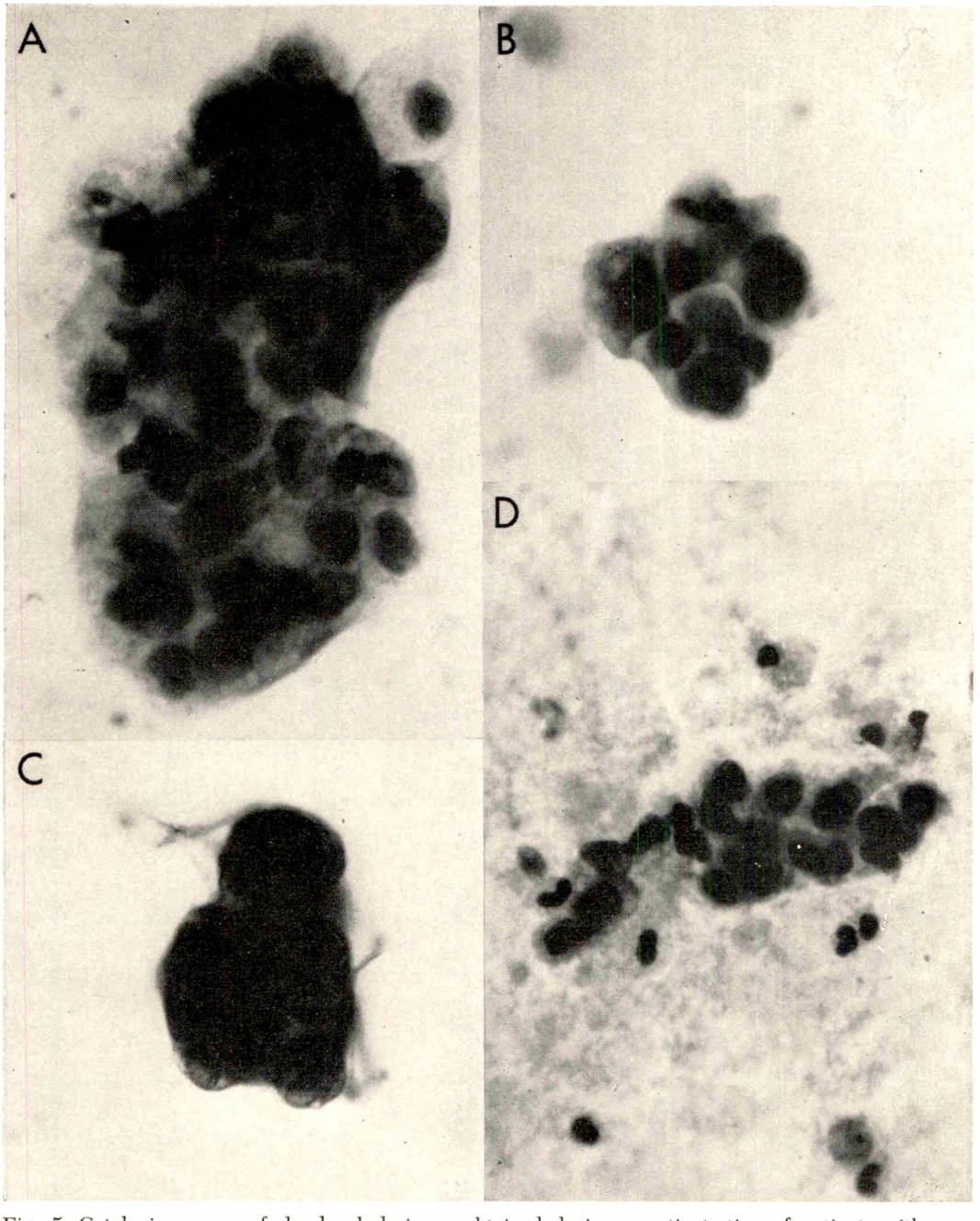


Fig. 5—Cytologic smears of duodenal drainage obtained during secretin testing of patients with cancers of (A) head, (B) and (C) body and (D) tail of the pancreas.

of smears (Fig. 5) but also upon the sophistication of the cytologist, the percentage accuracy is high, perhaps not as originally reported by Dreiling, et al,[10] i.e. between 80-85% but certainly above 70% (Table III). A positive cytology is very significant; a negative cytology does not completely exclude cancer. There is insuf-

TABLE III

CYTOLOGY FINDINGS IN DUODENAL DRAINAGE OBTAINED FOLLOWING SECRETIN FROM 104 PATIENTS WITH PANCREATIC CANCER

	No. of cases	Cytology positive	Per cent accuracy
Ca. of the head	50	42	82
Ca. of the body	38	34	89
Ca. of the tail	16	12	75
Total pancreatic ca.	104	86	83

ficient experience to determine whether or not examination of pancreatic duct fluid obtained by direct endoscopic aspiration will improve diagnostic accuracy.

The availability of pure pancreatic juice obtained directly from the duct of Wirsung during peroral endoscopy makes it possible to perform secretin tests on pancreatic secretion uncontaminated by duodenal contents. Moreover, examination of this uncontaminated secretion for cancer cells as well as for specific cancer diagnostic indicators, e.g. CEA, pancreatic specific RNase,[11] immunoglobulins A&M,[12] according to preliminary reports may prove of diagnostic importance in disclosing early pancreatic cancer. For example, examination of pancreatic juice in early pancreatic cancer reveals excessively high levels of IG-M whereas in late pancreatic malignancy IG-A is competely absent from pancreatic secretion. These findings are discretely different from the data of those without pancreatic disease as well as those with pancreatic inflammations (Fig. 6).

The isolation of CCK-PZ, of other hormones of the APUD system and the recognition of such pancreatic ecbolic agents as cerulein have resulted in a large number of modifications of the standard secretin test protocol. These are summarized in Table IV.

These modifications permit a large number of variations of specific stimulus, strength of stimulus, mode of administration and parameter of description. There results a bewildering array of data from many sources obtained from different protocols without sufficient numbers of comparability to assess reproduciblity and diagnostic value. In recent years, there has been a coalescence towards the procedures of Hartley, et al[13] employing "maximal" dosage of secretin and CCK-PZ and of Ribet et al[14] using a bolus of CCK-PZ superimposed upon a continuous infusion of secretin. These protocols are well designed and are likely to provide reproducible and comparable data.

There is the impression in the literature that the secretin test data conflict with the secretory findings obtained with CCK-PZ combined tests. Using secretin, the enzyme data is of lesser importance in diagnosis than fluid and electrolyte, a not surprising finding since secretin does not challenge the enzyme secretory parenchyma; using CCK-PZ, the significance of fluid and electrolyte tend to be subordinate to enzyme concentration and output, a result in many instances from protocol design. The limited experience of Dreiling, et al[15] with combined tests is often cited in this controversy. From this study of 55 patients using the secretin/CCK-PZ standard dose bolus technic and more than 300 patients using the CCK-PZ/secretin sequence standard dose bolus protocol, it was concluded that the enzyme data added little to diagnostic accuracy and that the fluid and electrolyte findings, even with the interference of the ecbolic stimulant, remained the most reliable diagnostic descriminate

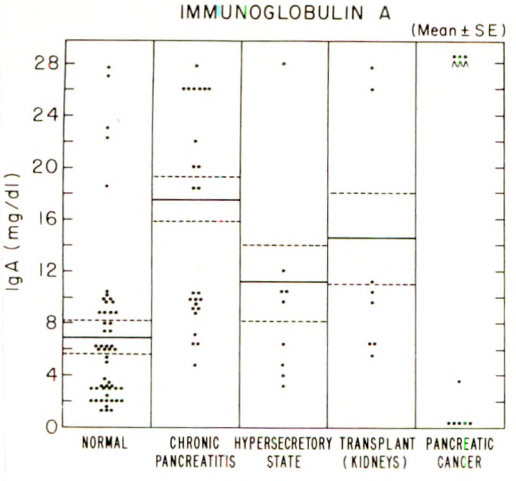


Fig. 6a

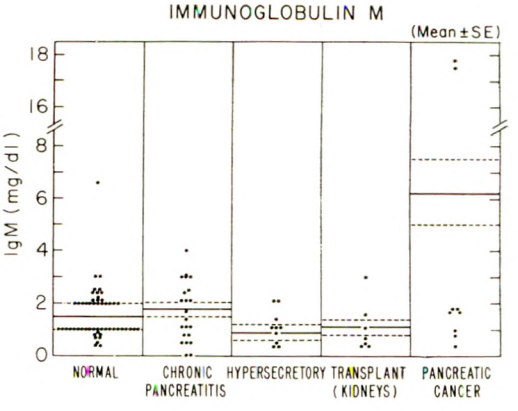


Fig. 6b

Figs. 6a and 6b—Immunoglobulin A and M concentration data in patients with and without pancreatic disease showing abnormality of value and distribution in pancreatic cancer.

parameters. But these studies were performed with an impure secretin containing small amounts of CCK-PZ and an impure CCK-PZ containing large amounts of secretin, i.e. about 25 U. secretin/100 U. CCK-PZ, a condition which might very well account for the differences in results from those observed later with purer preparations. It seems likely that pancreatic function can be as accurately defined and pancreatic disease diagnosed as well by the combined tests, be they more cumbersome and more expensive, as by the simpler secretin test techniques.

Of particular clinical interest have been stimuli of strength different from that used in the standard test, i.e. 1 clin. U./kg. which is a submaximal stimulus. The use of augmented stimulation is designed towards quantitation of the secretory mass[16-19] based upon the assumption that secretory mass would show correlation with extent of pathology and severity of complaint. The difficulty in defining a maximum secretory capacity is that, in man, it would require the combination of at least three stimuli, i.e. secretin-like, CCK-PZ-like and vagomimetic, as well as titration at sequential doubling of stimulus. Even for the simplest augmented test, the single bolus secretin test, the augmented dose has been reported to be quite different by different investigators, viz 2.0 clin./kg. to 14.0 clin. U./kg. While part of this discordance may result from variation in secretin preparation potency, the remainder must derive from individual differences in sensitivity as well as differences in protocol.

Using a single bolus augmented dose, 4.0-5.0/U./kg., it is possible to construct a 2 σ range in normal patients[20] (Table V). Employing this range, it is possible to interpret the secretory findings in patients with pancreatic disorders according to the patterns of secretion utilized in the standard secretin test. Preliminary reports[20] have confirmed, in over 750 patient studies, the observations that the augmented test: 1. augments the qualitative and quantitative secretory defects in patients with chronic pancreatitis and pancreatic cancer, respectively; 2. permits the scrutiny of two additional diagnostic parameters, i.e. fixation of flow and fixation of bicarbonate

TABLE IV

RECENT MODIFICATIONS OF SECRETIN TEST TECHNICS

1. Changes in technic
   a. Various hormonal combinations
   b. Test meals
   c. Synthetic hormones
2. Changes in technic of stimulant administration
   a. Subcutaneous
   b. Continuous infusion
   c. Intraduodenal
3. Changes in strength of stimulus
   a. Fixed dosage
   b. Augmented dosage
4. Changes in parameters determined
   a. Intraduodenal lipase and trypsin
   b. Fecal lipase and trypsin
   c. Duodenal pH

concentration; 3. permits the determination of secretory capacity in patients with marked secretory defects; 4. is useful in confirming diagnosis in patients with borderline secretory defects and 5. affords a means of evaluating the effectivenesss of resectional surgery for patients with pancreatic disorders and the degree of pancreatic regeneration.

When the secretory data of in-tandem standard and augmented secretin tests are compared, parameter for parameter, differences in the response pattern are observed between the patients without pancreatic disease and those with pancreatic cancer (Table VI). This fixation of bicarbonate and flow responses enhanced the functional borderline or abnormal secretion evident from the standard test. In patients following subtotal pancreatic resection or with total deficiency patterns, the secretory data, is illustrated in Table VII, were identical following standard and augmented stimulation, suggesting these secretory findings indicated a true maximum secretory capacity or a tubular secretory mass. In

TABLE V

2 σ NORMAL RANGES CALCULATED FROM THE AUGMENTED SECRETIN TEST DATA OF 130 PATIENTS WITHOUT PANCREATIC DISEASE

	Range	Lower limit
Volume ml./kg.	4.5-8.1	4.5
Maximum HCO_3 concentration mEq./l.	93-141	93
Amylase secretion U./kg.	8.3-65.1	8.3

these patients, it is obvious, the standard dose, 1.0/kg., applied to the remaining 20-25% of the pancreas, effectively stimulates the parenchyma at the augmented level of 4.0 U./kg. Thus, no increase in secretion can be anticipated with stimulation at 4.0 U./kg. secretin.

The measurement of pancreatic secretory mass is quite useful in the sequential testing of patients following resection. In the successful case, the clinical improvement can be shown to be paralleled by an increase in secreting parenchyma so that at the end of two to three years, the secretory capacity may not only return to preresectional levels but surpass these, objective evidence for pancreatic regeneration (Figure 7). There is every likelihood, that in man, as in the experimental animal, with an appropriate CCK-PZ-like stimulus and an appropriate protocol, a maximum enzyme secretory capacity for acinar mass will be defined and be of similar import in evaluation of pancreatic function.

On the other hand, there are interesting pancreatic secretion procedures involving "weak" stimuli. In general these have used an oral test meal to stimulate the gland indirectly by excitation of the trigger

TABLE VI

PERCENTAGE IN SECRETIN TEST DATA FOLLOWING STANDARD AND AUGMENTED SECRETIN TESTS PERFORMED IN PATIENTS WITH AND WITHOUT PANCREATIC DISEASE

	Volume ml./kg.	Maximum HCO_3 Concentration mEq./l.	Amylase secretion U./kg.
Normal patient	100%	10%	30%
Chronic pancreatitis	40%	Fixed or decrease	30%
Pancreatic cancer	15%	10%	30%

zone to pancreatic secretion, i.e. the duodenum-jejunum, which in turn releases secretin, CCK-PZ, etc. and/or elicits duodenopancreatic reflexes which initiate secretion. Three major objections have been raised against the oral test meals: 1. weak stimuli are difficult to quantitate; 2. the gastric secretory capacity and rate of evacuation may significantly influence the result and 3. the stimulus and gastric secretions are mixed in the duodenum with intestinal and biliopancreatic secretions so that evaluation of pancreatic flow and bicarbonate is difficult and quantitative estimation of enzyme secretion inaccurate.

Test meal technics evaluate pancreatic function in the physiologic sense of digestive capacity rather than secretory capacity, activities which in diseased or postoperative states might be quite different. For example, Lundh and Borgström,[21] in 1962, described a test of normal and abnormal digestive function using the oral administration of a test meal composed of milk protein, corn oil and dextrose. Following this, the concentration of trypsin is determined sequentially in duodenal aspirates. Low trypsin levels indicate pancreatic digestive insufficiency. Thus, postgastrectomy Billroth II, the Lundh test would be abnormal indicating inappropriate mixing of foodstuffs in the duodenum and inadequate release of secretin; the secretin test would be normal indicating a pancreas which could respond to appropriate excitation.

Recently, Tuzhilin and Dreiling[22] have used an intraduodenal "test meal" and compared the data with standard secretin test findings in order to contrast the secretory responses to both weak and strong stimuli in the same patient. After a standard secretin test, 4 mEq. HCl was instilled into the duodenum in 30 ml. In patients with pancreatic edema, the test meal revealed a new pattern of secretion, proximal blocked secretion (P.B.S.), i.e. low flow, low bicarbonate, high enzyme. Reversal of this response by submaximal stimulation, i.e. standard secretin, or diuresis indicated functional disorder; persistence, organic disease. If these preliminary findings are confirmed, the sequence of secretory change paralleling the progression of pathology would be as follows: 1. edema → P.B.S.; 2. minimal inflammation → hypersecretion; 3. moderate chronic inflammation → quantitative deficiency; 4. advanced chronic inflammation → *total deficiency.*

MECHANISMS OF PANCREATIC SECRETIONS AND PHYSIOLOGIC STUDIES

The availability of secretin, initially and then of CCK-PZ enabled studies elucidating the mechanisms of secretion by the pancreas to parallel the early studies employing these hormones in diagnosis. In general there were two avenues of investigation: 1. that clarifying the extrusion of enzymes and; 2. that describing the secretion of bicarbonate and water by parenchyma.

The elaboration and secretion of enzyme by the gland was clearly a func-

TABLE VII

STANDARD AND AUGMENTED MEAN SECRETORY DATA FROM TESTS PERFORMED IN-TANDEM IN NINE PATIENTS FOLLOWING 70-80% RESECTIONS OF THE DISTAL PANCREAS

	Volume		HCO_3		Amylase secretion
			Concentration	Secretion	
	ml./80 min.	ml./kg.	mEq./l.	mEq./80	U./kg.
Standard (1.0 U./kg.)	109	1.7	62	6.9	8.4
Augmented (4/0 U./kg.)	112	1.8	61	6.7	6.0

tion of the acinar cells, since only these possessed enzyme granules. The classical studies of Hokins and Palade on the steps of enzyme production and the mechanism of secretion earned them a Nobel Prize in Medicine.

At first, it was far from clear as to which cells produced water and bicarbonate. Yet, only the centro-acinar cells and ductular cells continued carbonic anhydrase, an intracellular enzyme which appeared necessary for the production of bicarbonate. From their extensive investigations in Thomas cannula canine preparations on the effects on the secretion of fluid and electrolyte of diamox,[23] a carbonic anhydrase inhibitor, anticholinergics,[24] ADH[25] and other diuretics; from the data observed in animals following administration of steroids,[26] ethionine[27] (which selectively destroyed the acinar cells), alloxan[28] (which selectively destroyed the ductules) and from classical stop-flow analysis[29] of pancreatic secretion following secretin, Dreiling and Janowitz[30-32] demonstrated that: 1. the centro-acinar and proximal ductular cells secreted water and bicarbonate; 2. the ductular system was not a passive conduit carrying secretion from acinus to duodenum; 3. as the fluid progressed down the duct system it underwent a change in composition involving an interchange of HCO^-_3 and chloride (Cl^-) the magnitude of which depended upon the rate of flow, the cross-sectional area of the duct system (dilation), the presence or absence of obstruction (stasis), the integrity of the ductal epithelium and the relative mass of the acinar parenchyma to that of the ductular tissue. This mechanism of secretion is illustrated in Figure 8.

These data clarified the secretory defect in chronic pancreatitis wherein ductal hyperplasia, ductal ectasia, ductal dilation and ductal obstructions all combined to augment the interchange of chloride and bicarbonate so that the juice reaching the duodenum would contain a lower bicarbonate content than that in the normal patient at the same rate of fluid flow.

Other physiologic studies of secretion also yielded data of clinical importance. First, it was shown that both vagisection[33] and subtotal gastrectomy[34] inhibited pancreatic secretion, observations which ultimately suggested selective and supraselective vagisection without gastric resection as more physiologic procedures in the treatment of peptic ulcer. Then, there were extensive investigations concerning the effect of various extraenteric hormones on pancreatic secretions. Investigations indicated that

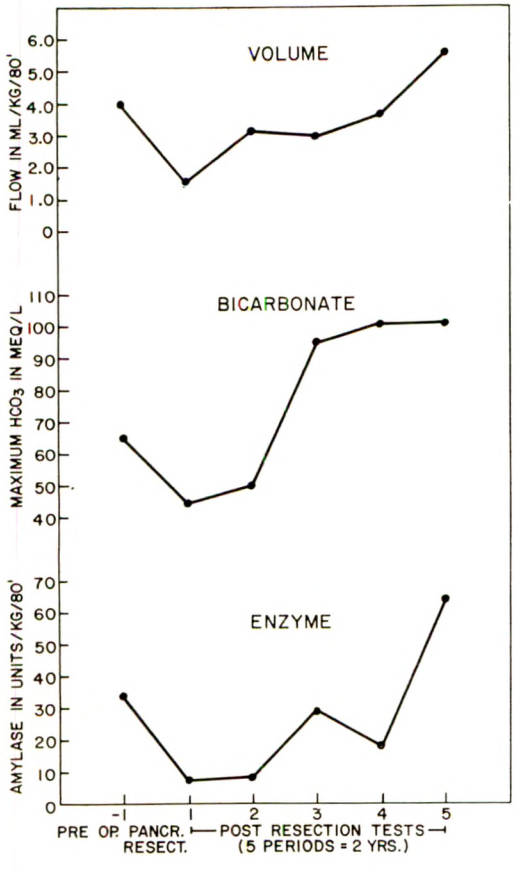


Fig. 7—Sequential secretin response data before and after major pancreatic resection (extended DuVal) illustrating regeneration with augmentation of secretory capacity and secretory mass.

not only the administration of these hormones, i.e. ACTH,[35] steroids,[36] thyroxin,[37] estrogens,[38] progesterone,[38] prolactin,[38] etc. but also extirpation of the respective endocrine gland, inhibited pancreatic secretion. From these data derived the concept of substances trophic to the pancreas, originally ACTH and growth hormone but now known to include CCK-PZ, gastrin, and trypsin,[39] all of importance in pancreatic regeneration and repair. Another clinical dividend of these physiologic studies of hormonal inhibition of pancreatic secretion was insight into the suppression of secretion during pregnancy and the pathogenesis of the pancreatitis of pregnancy.[40]

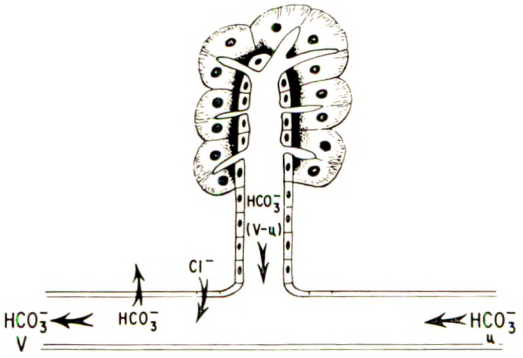


Fig. 8—Diagram of electrolyte interchange occuring in pancreatic duct as secretin passes from acinus to duodenum.

Finally, physiologic studies involving the effects of glucagon,[41] prostaglandins[42] and their analogs[43] and various beta-adrenergic blocking agents,[44] revealed that all inhibited pancreatic secretion. Of these, the beta-adrenergic blockers and glucagon have been tried in the treatment of experimental and clinical acute pancreatitis and have been found ineffective. Administration of prostaglandins in the treatment of pancreatitis has been delayed by the lack of a long acting analog but should be given clinical trial now that such is available.

It has been recently shown that in the experimental animal as well as in man, parenteral alimentation suppressed pancreatic secretion.[46] This observation was effectively incorporated into the treatment of acute pancreatitis, wherein such alimentation not only splints the pancreas but maintains a positive nitrogen balance, a state beneficial to the profound shock in acute pancreatitis.

Pathogenesis of Pancreatic Inflammation

Secretin, secretin testing and secretin-determined pancreatic secretory capacity

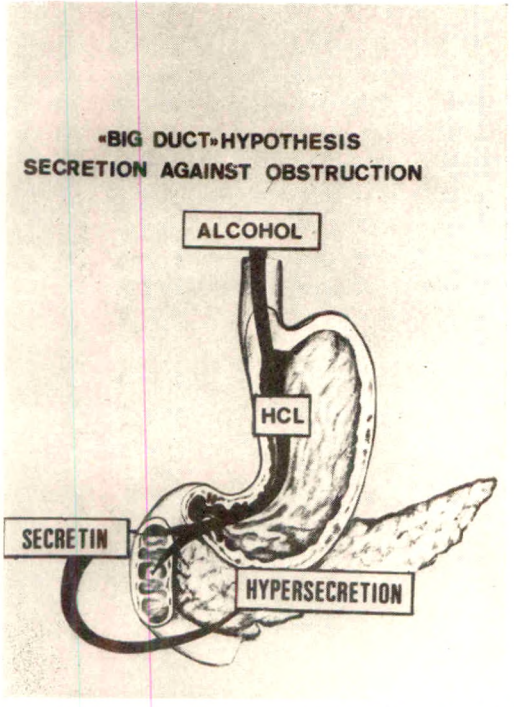


Fig. 9—"Big Duct" hypothesis of pathogenesis of pancreatitis.

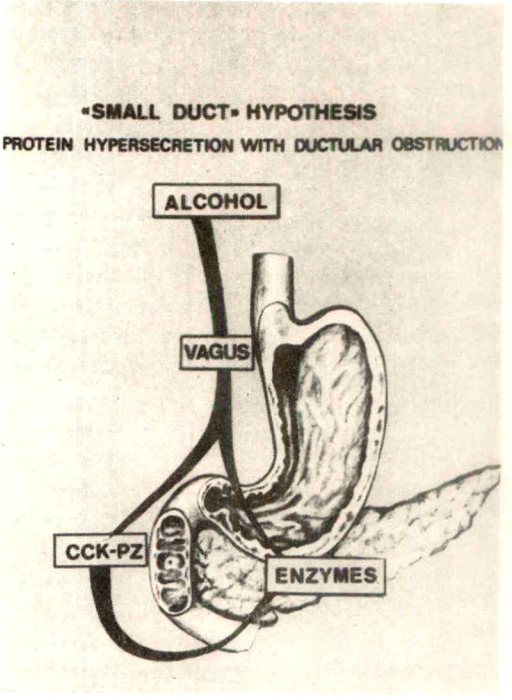


Fig. 10—"Small Duct" hypothesis of pathogenesis of pancreatitis.

have played a crucial role in the elucidation of pathogenesis of pancreatitis. The classical concepts of common channel and biliary reflux[47] were persistently challenged by data which indicated that 1. a common channel was not a *sine qua non* for pancreatitis; 2. biliary regurgitation was unlikely since secretory pressures were always higher in the pancreatic ductal system than in the common duct.

Evidences derived from: 1. anatomic studies of the peri-ampullary area; 2. experimental varieties of pancreatitis and 3. clinical correlations of pancreatitic inflammation, appeared to implicate pancreatic ductal obstruction as the initial etiologic factor in the induction of pancreatitis. Thus rose the "Big Duct Hypothesis" which postulated that pancreatic inflammation resulted by a stimulated gland secreting against obstruction (Fig. 9). The increased intraductal pressure would result in rupture of the duct with extravasation of activated pancreatic enzymes particularly trypsins and lipases into the interstitial tissues, gradually exhausting natural enzyme inhibitors and producing chemical inflammation with autodigestion. For the alcoholic variety of pancreatitis, the big duct hypothesis stipulated that: a. alcohol entering the stomach induced a copious flow of HCl; b. HCl, in the duodenum, released secretin which stimulated the gland to secrete against; c. the obstruction caused by the local inflammatory response, viz. edema of the duodenal mucosa and particularly the papilla of Vater due to alcohol.[48]

This attractive hypothesis was accepted for years despite its failure to explain: 1. the rarity of an attack of acute pancreatitis following an initial overindulgence in alcohol; 2. the observed long "latent" period of five to seven years following the onset

TABLE VIII

POSTSECRETIN DATA OF PATIENTS WITH PANCREATIC HYPERSECRETION

	No.	Average 80 min. flow ml./kg.	Average maximum HOC_3 mEq./l.	Average 80 min. HOC_3 secretion mEq.
Alcoholism	28	4.9	95	30.6
Biliary cirrhosis	44	4.4	108	32.4
Nonalcoholic cirrhosis	39	4.5	106	36.5
Alcoholic cirrhosis	95	6.2	94	43.2
Hemachromatosis	19	9.4	96	60.9
Upper limit normal		4.0	130	30.0

alcoholism in which continued excessive drinking was required to induce acute pancreatitis and 3. the observation that in some patients, the secretin test data returned to normal following recovery from acute pancreatitis, while, in others, the data was characteristic of chronic pancreatitis.

Tiscornia, working in Sarles laboratory,[49] studying the pancreatic secretion following secretin and CCK-PZ in dogs made alcoholic, evolved an alternate hypothesis. Alcohol released excessive amounts of CCK-PZ, incited vagotonia and increased the sensitivity of the acinar cell to hormonal stimulation resulting in increased protein (enzyme) secretions which precipitated as plugs in the small ducts, effectively producing small duct obstruction. This "Small Duct Hypothesis" (Fig. 10), however, did not account for the three criticisms directed towards the "Big Duct" theory. It remained for elucidation of pancreatic hypersecretory states and for secretin test data indicating regeneration of pancreatic secretory capacity following injury to resolve the three enigmas.

Although, initially, the secretory pattern, discordant secretion, characteristic of hemochromatosis was not understood, experience with secretin testing indicated that pancreatic hypersecretion occurred in other conditions, e.g. cirrhosis, Zollinger-Ellison syndrome and even alcoholism without manifest cirrhosis or pancreatitis (Table VIII).[50] Studies with secretin showed that the increased flows were due to: 1. increased pancreatic ductular mass-alcoholic pancreatitis (early); 2. increased hepatic ductular mass-cirrhosis; 3. increased ductular mass in both organs/hemochromatosis; 4. synergism between gastrin and secretin/Zollinger-Ellison syndrome.

The unexpected finding was hypersecretion in alcoholics without manifest cirrhosis or manifest pancreatitis. Additional information was gained by study of the raw secretin data of patients with chronic alcoholic pancreatitis (Table IX) and by plotting frequency distributions of flows in chronic alcoholic pancreatitis (Fig. 11). These studies clearly indicated that in early alcoholic pancreatitis the pattern of secretion was hypersecretion; as the pathology progressed the secretin response showed decrease in flow and decrease in bicarbonate yielding the qualitative pattern of

TABLE IX

POSTSECRETIN DATA OF PATIENTS WITH CHRONIC PANCREATITIS

	No.	Average flow ml./kg./80 min.	Average maximum HCO_3 concentration mEq./l.	Average HOC_3 secretion mEq./80 min.
Alcoholic pancreatitis	204	2.6	56	6.4
% Above lower limit		67%	2%	12%
% Above upper limit		14%	0%	0%
Biliary tract pancreatitis	104	2.9	64	7.8
% Above lower limit		75%	2%	14%
% Above upper limit		21%	0%	0%
Alcoholism	28	4.9	95	30.6

normal flow and low bicarbonate. Continued inflammation resulted in continued decrease in flow and bicarbonate to the pattern of total deficiency or low volume-low bicarbonate. These observations explained the inability to show good correlation between secretin test findings, ERCP and the pancreatic histology in patients subjected to pancreatic resections for pain.[52]

In man, the pancreas is not easily accessible to serial biopsies. Therefore, sequential steps from the initial morphologic lesion to the late stages of pancreatic cirrhosis have been difficult to describe. Recently, Bordalo and Dreiling[53] reported the results of an investigation designed to elucidate the pathologic alterations in the pancreas which were associated with the temporal changes in clinical symptoms and secretory response. Pancreatic specimens obtained with informed consent were studied by light, thin section and electron microscopy. The surgical biopsies were performed in the most grossly normal areas of the gland in patients without pancreatitis, with nonalcoholic pancreatitis, chronic alcoholics without pancreatitis and in patients with chronic alcoholic pancreatitis. The histologic alterations observed in alcoholics with and without pancreatitis included: 1. fat droplet accumulation in the cells (Fig. 12a); 2. ductular reduplication and periductular fibrosis; 3. endoplasmic reticular hyperplasia (Fig. 12b); 4. mitochrondrial distortion.

These findings are identical to those observed in the liver in response to chronic injury by alcoholism.

The fat droplets varied in size from small to big cyst-like vacuoles. The cells with fatty degeneration displayed a parallel decrease in zymogen granules. Less frequently, centro-acinar and ductular cells showed fatty accumulation but without evidence of cell degeneration. Signs of ductular reduplication were present and periductular fibrosis was occasionally found. In general, the lobular architecture was preserved.

Electon microscopy reveals the ultrastructural changes, i.e., dilatation and vesiculation of the endoplasmic reticulum (Fig. 13a). The cells frequently contained a fibrillar curved osmeophylic material as-

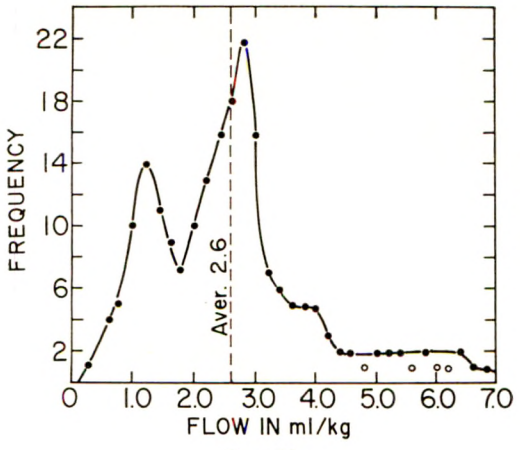


Fig. 11a

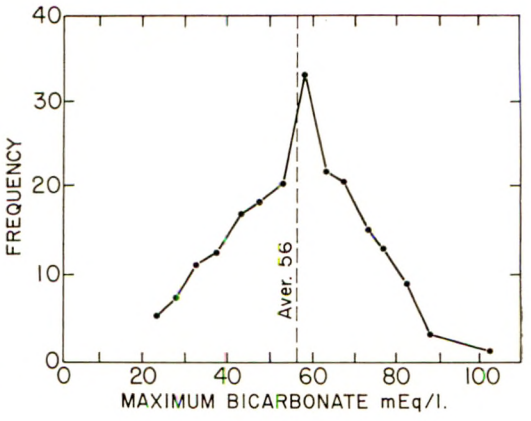


Fig. 11b

Figs. 11a and 11b—Frequency distribution curves for flow and bicarbonate concentration in patients with alcoholic pancreatitis.

suming the appearance of myeline-like fibers, surrounded by an irregular clear area of granular substance (Fig. 13b). Less frequently, the mitochondria were enlarged and revealed distortion of the mitochondrial cristae. The greater the alcoholic consumption the more conspicuous the abnormalities found.

Light and thin section specimens taken from patients with chronic pancreatitis disclosed in addition to these abnormalities: 1. acinar atrophy; 2. signs of ductular hypertrophy and metaplasia; 3. areas of periductular and septal fibrosis.

These findings, although focal, disturbed the normal architecture of the gland.

Acinar ultrastructure in the patients with chronic alcoholic pancreatitis showed increased incidence and prominence of the alterations described for the alcoholics without pancreatitis. The organelle lesions were most apparent in the acinar cells; ultramicroscopic alterations of the ductular cells were minimal.

Based on morphology it seems evident that the first response of the pancreas to alcoholic injury is fat accumulation within parenchymal cells. This could be due either to a direct toxic effect of ethanol, through a metabolic pathway, such as in the liver, or to an indirect effect, by means of an alcohol-induced hyperlipemia.

The data indicate the acinar cell to be the structure primarily affected by chronic ingestion of alcohol. Fatty accumulation may initially be a normal and appropriate response and, therefore, reversible (Fig. 14). Signs of cellular degeneration and decrease of zymogen granules appear with increasing fat droplets. At this stage of the pathology, small amounts of fat may appear within ductular cells. Ultrastructural changes, especially those in the endoplasmic reticulum, could represent not only the toxic effect of alcohol on cytomembranes as it is found in the liver of alcoholics but also an inhibition of synthesis of polypeptides on membrane-bound polyribosomes.

Ductular reduplication may represent the reaction of the cell to fat accumulation or result from a direct toxic effect of alcohol. This morphologic step is responsible for fluid and bicarbonate hypersecretion (Fig. 15).

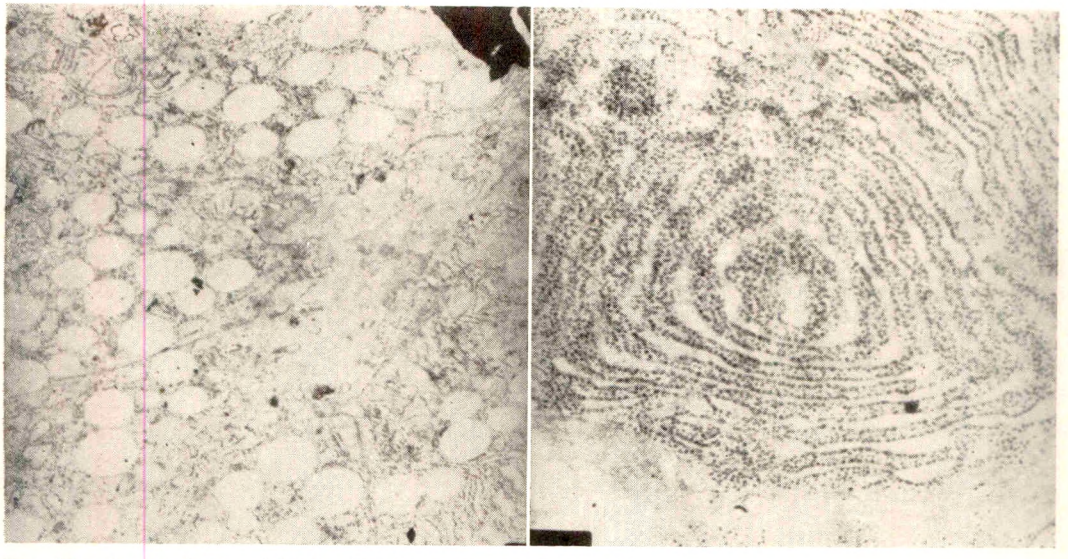


Fig. 12a—Accumulation of fat droplets in pancreatic acinar cell.

Fig. 12b—Endoplasmic reticular hyperplasia of pancreatic acinar cell.

Development of extensive fibrosis around ducts as well as ductular hypertrophy and reduplication causes ductular obstruction, stasis and, therefore, protein plug formation.

Finally, distortion of the glandular architecture in addition to continuing ductular obstruction results in atrophy of acinar tissue and metaplasia of ductular cells with its pattern of pancreatic insufficiency (Fig. 16).

Thus, it has been possible with data accumulated from secretin testing to progress from the initial hypothesis of pathogenesis, i.e. "common channel", through "biliary reflux", the "big duct" theory, the "small duct" thesis, to the modern toxic metabolic hypothesis of alcoholic pancreatitis.

Pancreatic Contribution or Involvement in Various Gastrointestinal Disorders

The availability of secretin and secretin test data has made a significant contribution to clinical medicine by elucidating the pancreatic contribution and/or involvement in various gastrointestinal disorders.

These tools made it quite simple to determine whether or not pancreatic dysfunction played a significant role in the postcholecystectomy[54] and postgastrectomy syndromes.[55] In the former, pancreatitis and pancreatic cancer were rarely encounted; in the latter, although the pancreatic secretion in response to secretin was normal, the Lundh test indicated a deficiency in digestive capacity due to poor secretin-release and inadequate mixing of foodstuffs with bile and pancreatic secretion. The steatorrheas encountered in ulcerative colitis, granulomatous enteritis and sprue could now be evaluated.[56] The data indicated that, in about 10% of these patients, pancreatic insufficiency contributed to the steatorrhea. The pancreatic deficit was, at first, presumed to be nutritional, probably due to protein starvation. But no such deficiencies were encountered in patients equally malnourished from various malignancies and other chronic debilitating diseases. Moreover, when patients kept on a

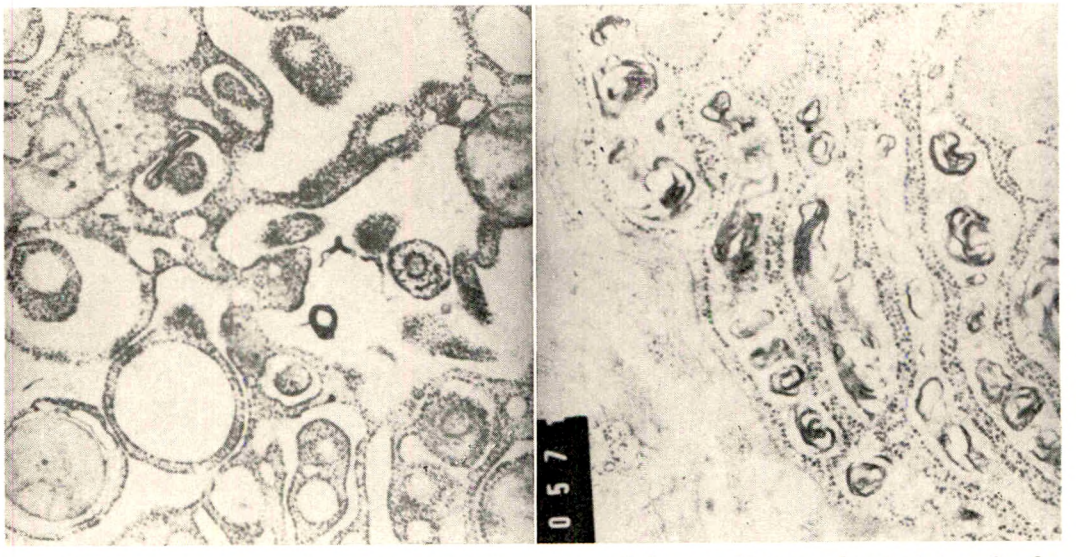


Fig. 13a—Electron microscopic section pancreatic acinar cell showing dilation and vesiculation of endoplasmic reticulum.

Fig. 13b—Electron microscopic section pancreatic acinar cell.

10 gm. protein/day diet for a year were studied sequentially, with secretin, pancreatic secretion did not deteriorate.[57] It is now generally accepted that the pancreatic fibrosis in these disorders derives from absorption of toxic products of bile acid degradation. The steatorrheas and digestive complaints observed in patients with Sjögren syndrome and scleroderma[58] have a more complex origin. Pancreatitis and pancreatic fibrosis occur in over one-third of these patients and result not only from participation of the pancreas in the pathology of the disease but also from pancreatic ischemia, as well as from the medications employed to treat the illness, e.g. steroids, antimetobolites and antibiotics, all of which appear to be toxic to the gland. Vascular lesions as seen in *Lupus erythematosus*, disseminated sclerosis, *periarteritis nodosa*[59] and migratory phlebitis[60] have been shown by secretin tests to be compilcated by pancreatitis and, even pancreatic cancer. Concerning pancreatic cancer, clinical association with thrombophlebitis has been generally accepted; its association with pancreatic inflammatory disease was unsuspected until clinical studies with secretin. Secretin test data have even disclosed a clinical association of pancreatic calcification and pancreatic cancer, an incidence of 25% being reported in one series.[61] Finally, on the other hand, the secretin test has been useful in disproving a suggested clinical association, viz. the hypothesis that chronic pancreatitis, pancreatic insufficiency malabsorption of essential fats was an etiologic factor in amyotropy lateral sclerosis. A study of 14 successive patients with this disorder displayed no pancreatic insufficiency.[62]

A pancreatic factor in the pathogenesis of peptic ulcer diatheses has been proposed by many physiologists.[63] It remained for secretin test data to demonstrate that pancreatic deficiency did not contribute to the duodenal hyperacidity of duodenal ulcer or even Zollinger-Ellison syndrome wherein, if anything, the pancreatic secretory capacity is enormously increased.[65]

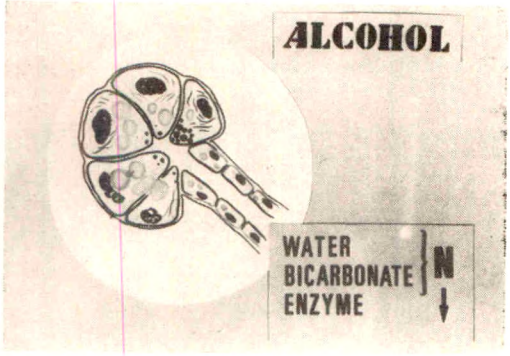


Fig. 14—Initial response of pancreas to alcohol-fatty globule accumulation.

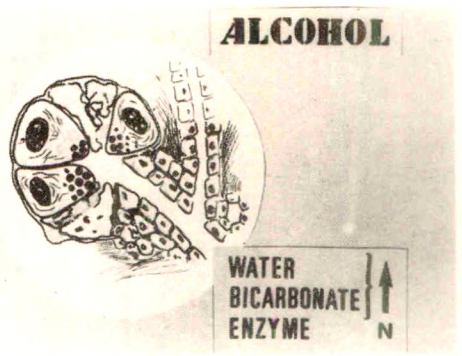


Fig. 15—Ductular reduplication and the phase of of pancreatic hypersecretion.

Secretin studies, moreover, did elucidate the deleterious effects of coffee and smoking on the clinical course of patients with peptic ulcer. These not only stimulate gastric acid secretion but depress for long periods the ability of the pancreas to secrete bicarbonate; both factors additive in increasing duodenal hyperacidity.[64] On the other hand, the occurrence of pancreatitis in patients with peptic ulcer was clearly shown to influence adversely the clinical course and the prognosis for cure after appropriate therapy.[63] While the increased incidence of peptic ulcer in patients with cirrhosis has been controversial, it is generally accepted that portocaval shunting does increase peptic ulcer diathesis. Secretin tests before and after shunting have presented a *raison d'etre* for this increased incidence, namely a suppression of pancreatic secretion following portocaval[66] and mesocaval[67] shunt. This increased incidence is not seen in splenorenal shunting which to the contrary, increases pancreatic responsiveness. The latter shunt then would provide better neutralization of acid following portal decompression in cirrhotics with high gastric acid secretion.[67]

Studies with secretin have provided much information concerning the pancreatitis associated with pregnancy, a complication of the third trimester and postpartum. A variety of factors: 1. increases in ACTH,[68] growth hormone, corticosteroids;[36] 2. increase in estrogen, progesterone, prolactin;[69] 3. increase in ADH[25, 70] and antidiuretic therapy,[23] all combine to inhibit and concentrate pancreatic secretion at this time. The decreased flow of a concentrated juice, stasis in the ducts and precipitation of protein plugs will produce small ductal obstruction and result in pancreatitis.[40]

Secretin test data have been particularly useful in the treatment of patients with pancreatic inflammation or with pancreatic related syndromes. For example, the findings clearly indicated no therapeutic benefit from: 1. diamox;[31] 2. ACTH and cortisone;[26] 3. anticholinergics;[24] 4. Trasylol;[71] 5. glucagon[41] in patients with acute pancreatitis.

On the other hand, parenteral alimentation[46] has been proved to be of value in the suppression of pancreatic secretion. X radiation of the pancreas has also been advocated to splint the pancreas. Physiologic studies, however, revealed that suppression of pancreatic secretion by x-ray occurred only after a latent period of about one month and that this suppression tended to be permanent.[72] Indeed, the effect on the pancreas of abdominal radiotherapy

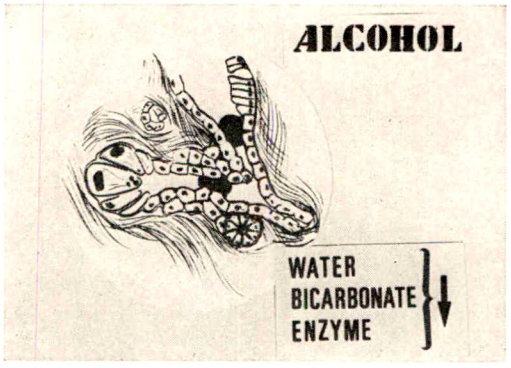


Fig. 16—Small duct obstruction, protein plugs, and pancreatic insufficiency.

given for malignancies may be important in postradiation digestive disorders.[72]

Evolution of the APUD Concept

Physiologic studies with secretin were crucial in the unravelling of one of the most complex feedback mechanism in the human body. The concept of a chemical messenger or hormone introduced by Bayliss and Starling[1] was revolutionary and resisted by the Pavlovian physiologists whose creed demanded that the autonomic nervous system be the ultimate regulator of metabolic and secretory processes.[73] After 75 years, some difficulty still remains in the integration between the neural and hormonal mechanisms as well as their precise role in human digestion and metabolism. From the most recent and sophisticated studies, physiologists at most can draw the following generalizations: 1. the neuroendocrine and gastroinestinal endocrine cells derive from a common zone of the fetus[74] (Fig. 17); 2. the neural and humoral regulatory mechanisms for gastrointestinal function act not separately but in close association;[74, 75] 3. the neural mechanisms tend to act as the heralds in digestion and often act to set the tone or sensitivity of the effector cells. In a sense the nervous system is the "course adjustment". 4. The humoral or gut hormonal

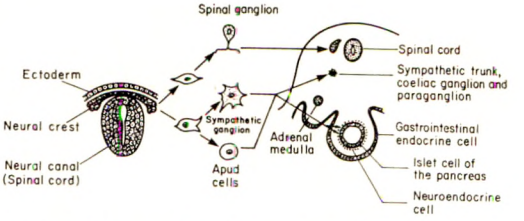


Fig. 17—Embryologic derivation of the neuroendocrine-APUD systems.

system is the fine adjustor, delicately responsive to stimuli within the gut and combining with the nervous system to comprise one of the most complex feedback mechanisms or cybernetic systems in the animal kingdom. The earliest studies of the gastrointestinal hormones focused upon secretin's physiologic activity and its clinical significance. To be sure crude secretin was known to have other active principles, e.g.: 1. pancreozymin; 2. cholecystokinin; 3. hepatocrinin; 4. enterocrinin.

Purification of principle and refinement by extraction from the duodenal mucosa soon revealed that pancreozymin and CCK were one hormone, i.e. CCK-PZ and that hepatocrinin activity was a property both of secretin and CCK-PZ.

While sophisticated refinements of testing with secretin were taking place, the gastrointestinal physiologist was being confronted with an increasing array of peptides and other compounds extracted from the gut and its derived organs, which, upon study, demonstrated, in addition to secretory activity, a variety of other effects.[76] Vigorous investigation by the biochemist defining molecular structure and intensive research by the immunochemist with radioimmune assay[77] have revealed that these active principles are secreted by a host of cells widely distributed in the gastrointestinal organs. These endocrine cells comprise the APUD system,[78] so named because of the following characteristics: 1. all secrete amines and/or polypeptides; 2. se-

cretory cells are not aggregated but dispersed widely in the gastrointestinal tract; 3. secretory cells are closely related to the gastrointestinal lumen; 4. releasing stimuli are either chemical or physical; 5. except for tumors there are no common hyposecretory or hypersecretory syndromes; 6. all have motility effects on the gut; 7. no stoichiometric relationships exist between plasma level and functional response; 8. all have APUD decarboxylase, i.e.: a. a high content of Amines; b. the capacity for amine Precursor Uptake and c. possession of an amino acid Decarboxylase for conversion of the amino acid precursors to amines.

It was obvious from the earliest studies that the end result of APUD hormonal activity was not merely the initiation of cellular secretion but rather a variety of additional effects which might be summarized: 1. stimulation or inhibition of secretion; 2. stimulation or inhibition of motility; 3. opening or closing of sphincters; 4. stimulation or inhibition of hormone release; 5. increase or decrease in membrane permeability; 6. change in electrolyte composition of secretion; 7. increase or decrease in vascular perfusion.

A listing of the known activities of secretin will illustrate the complexity of hormonal response. Secretin is now accepted as initiating various pharmacologic actions,[76] i.e. in the various organs, the following:

1. Parotid—stimulation of fluid and electrolyte.

2. Gastroesophageal sphincter—relaxation by competitive inhibition of gastrin.

3. Stomach
   a. inhibition of parietal cell secretion;
   b. relaxation of muscular activity;
   c. antitrophic.[19]

4. Duodenum
   a. stimulation of mucous secretion by Brunner glands;
   b. (?)relaxation of the spincter of Oddi;
   c. relaxation of muscular activity.

5. Pancreas
   a. stimulation of fluid and electrolyte;
   b. synergistic facilitation of enzyme response to pancreozymin;
   c. release of insulin;
   d. increase in blood flow.

6. Liver and Gallbladder
   a. alteration of hepatic fluid and electrolyte secretion;
   b. stimulation of water and bicarbonate by liver ducts;
   c. (?) relaxation of the gallbladder;
   d. increase in permeability of gallbladder mucosa.

7. Small and Large Intestines
   a. increase in mucosal transport of fluid and electrolyte;
   b. increase in secretion of fluid and electrolyte by intestinal glands;
   c. decrease in motor activity.

When one considers the total known membership of the APUD system, i.e.:

1. Foregut—Branchial Pouches
   a. Pituitary—Growth Hormone, ACTH, ADH
      Somatostatin
   b. Salivary—Glucagon
   c. Thyroid—Parathyroid—
      Thyroxin
      Parathormone
      Calcitonin?

2. Midgut
   a. Stomach

Gastrin
HCl(?)
Histamine(?)

b. Duodenum and Small Intestine
Gastrin
Secretin
Darmstadt(?)
CCK-PZ
Substance P(?)
Enteroglucagon
Enterokinin(?)
V.I.P.
Vilikinin(?)
G.I.P.
Serotonin(?)
Motilin
Bombesin

c. Pancreas
Insulin
Glucagon
Somatostatin
Gastrin

3. Hindgut
a. Adrenal
Adrenalin
Noradrenalin
Corticoids

b. Gonads
Estrogens
Testosterones
Progesterone
Prostaglandins

One can readily accept it as the most complex feedback or cybernetic system of the body whose total activities in digestion and metabolism might be summarized as follows:

1. Homeostatic
2. Ecbolic and Secretory
3. Muscular and Sphincteric
4. Cybernetic
5. Trophic
6. Absorptive
7. Vascular
8. Metabolic

It is obvious that comprehension of this complex system is only fragmentary. A number of important questions remain to be answered by the gastrointestinal physiologist, viz: 1. which polypeptides are artifacts of isolation and which are true hormones;[79] 2. which activities of the true hormones are pharmacologic and which are physiologic;[79] 3. what is the physiologic role and importance of the different hormones and their different activities;[80] 4. how are the endocrine and nervous mechanisms integrated in the normal and abnormal states.

When these questions are answered the processes of digestion will be better understood and the mechanisms of various gastrointestinal disorders elucidated with improvement in clinical diagnosis and treatment of a large number of tumors of this system with their fascinating aberrations of metabolism.[80]

Conclusion

The discovery of secretin, its use in experimental physiology, its application to clinical problems in medicine present an exciting chapter in the history of medicine!

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Elevated Serum Amylase Activity in the Absence of Clinical Pancreatic or Salivary Gland Disease

Possible Role of Acute Hypoxemia

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Elevated serum amylase activity, in the absence of clinically apparent pancreatic or salivary gland disease, has been observed in many seemingly unrelated conditions. In a search for common etiological factors to account for hyperamylasemia in these conditions, a retrospective analysis was performed. Eighty-four episodes of hyperamylasemia (> 300 I.U./l. Phadebas method) occurring in 75 patients over a one-year period ending in June, 1975 were assigned to one of two groups. Group 1 consisted of 56 (67%) episodes of hyperamylasemia with clinical pancreatitis. Group 2 consisted of 28 (33%) episodes of hyperamylasemia in the absence of clinical pancreatitis. Hypoxemia (pO_2 < 75 mm. Hg.) was found in 9/15 patients in Group 2 who had arterial blood gases measured. To assess the possible relationship between acute hypoxemia and amylase activity, a prospective study was initiated. Patients with known causes of pancreatitis or renal failure were eliminated. Hyperamylasemia was found in 3/8 hypoxemic patients. This raises the possibility that acute hypoxemia alone or in combination with other factors may raise serum amylase activity, possibly through ischemic injury to the pancreas or salivary glands or other amylase containing tissues.

Introduction

Multiple diverse conditions have been associated with hyperamylasemia in the absence of clinical pancreatitis and salivary gland disease. These include renal insufficiency, ruptured aortic aneurysm, pneumonia, codeine and morphine therapy, acute myocardial infarction, bronchogenic carcinoma, perforated duodenal ulcer, paralytic and obstructive ileus, acute appendicitis, ruptured ectopic pregnancy, mesenteric thrombosis, cerebral trauma, urinary tract infections, hemolysis, Meckel's diverticulitis, abdominal carcinomatosis

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TABLE I

CLINICAL ENTITIES ASSOCIATED WITH HYPERAMYLASEMIA WITH CLINICAL PANCREATITIS (GROUP 1)

Etiology	Number of cases			Number hypoxemic*/number who had blood gases assessed
	Male	Female	Total	
Alcoholism	7	2	9	2/2
Postoperative	8	7	15	6/7
Biliary tract disease	3	3	6	1/1
Perforated duodenal ulcer	2	0	2	1/1
Hyperlipidemia	1	1	2	1/1
Trauma	4	3	7	7/7
Carcinoma of the pancreas	0	1	1	1/1
Idiopathic	7	7	14	7/7
Total:	32	24	56	26/27

* Defined as $pO_2 < 75$ mm. Hg.

and splenic hemorrhage.[1-11] Elevation of the serum amylase in these latter conditions has received little investigative attention while the mechanism responsible for the rise in amylase activity in some of these conditions has been clarified to a degree, the pathogenesis of the hyperamylasemia in many of them is still virtually unknown. The purpose of this investigation was to examine the clinical background of all patients with hyperamylasemia during a one year period in search of possible common etiological factors.

METHODS

The medical records of 75 in-patients who experienced 84 episodes of hyperamylasemia at the Royal Victoria Hospital (Montreal) during a one-year period ending in June, 1975 were reviewed. An episode of hyperamylasemia was defined as elevation of the serum amylase greater than 300 I.U./l. on one or more occasions. It should be noted that the measurement of serum amylase activity is not part of the computerized biochemistry screen at the Royal Victoria Hospital but must be requested specifically. Serum amylase activity was determined by the Phadebas method and arterial oxygen levels were determined on an Instrumentation Laboratory Inc. pH Blood Gas Analyzer, Model 113. Amylase isoenzymes were separated as previously described.[12] Briefly, a serum sample containing 6×10^{-3} I.U. of amylase was subjected to polyacrylamide gel electrophoresis and the position of the enzymatic amylase activity was visualized by iodine development of a starch agar film that had contacted the column for 6 hours at 37° C.

Each episode of hyperamylasemia was assigned to one of two groups: Group 1—hyperamylasemia with clinical pancreatitis; Group 2—hyperamylasemia in the absence of clinical pancreatitis. The diagnosis of pancreatitis was made on the basis of clinical criteria, laboratory data, radiographic findings, hospital course and operative and autopsy material, where available. Each case was reviewed thoroughly

TABLE II

CLINICAL ENTITIES ASSOCIATED WITH HYPERAMYLASEMIA IN THE ABSENCE OF CLINICAL PANCREATITIS (GROUP 2)

Etiology	Number of cases			Number hypoxemic*/number who had blood gases assessed
	Male	Female	Total	
Alcoholism	2	0	2	0/1
Postoperative	7	3	10	4/5
Renal failure**	3	0	3	1/1
Bowel infarction	2	0	2	1/2
Hepatitis	0	1	1	0/0
Trauma	4	0	4	1/3
Pneumonia	1	0	1	1/1
Abdominal carcinomatosis	0	1	1	0/0
Acute myocardial infarction	1	0	1	0/1
Idiopathic	1	2	3	1/1
Total:	21	7	28	9/15

* Defined as $pO_2 < 75$ mm.
** Defined as BUN > 50 mg.% and/or Cr > 2.0 mg.%.

and classified with respect to common known, or presumed etiological factors.

RESULTS

Retrospective study:—Group 1, hyperamylasemia in the presence of clinical pancreatitis, consisted of 56 episodes in 30 males and 19 females. The mean age of the patients was 49 years. Maximum serum amylases ranged from 342-9,400 I.U./l., with a mean of 1,859.

Group 2, hyperamylasemia in the absence of clinical pancreatitis, or salivary gland disease consisted of 28 episodes in 18 males and seven females. The mean age was 51 years. Maximum serum amylase ranged from 318-5,250 with a mean of 776 I.U./l. The serum amylase determinations reported were those requested by the patients' physicians in the context of normal diagnosis and management.

The clinical entities associated with hyperamylasemia in patients with and without clinical pancreatitis, corresponding to Groups 1 and 2, are listed in Tables I and II, respectively. A thorough review of all cases in Group 2 was performed in a search for common etiological factors to account for the elevation of serum amylase activity in the absence of apparent pancreatic or salivary gland disease. It was noted that nine of 15 patients in this group, who had arterial blood gas measurements, were hypoxemic ($pO_2 < 75$ mm. Hg.) within two days prior to, or at the same time as hyperamylasemia was recorded. The clinical conditions and/or disease processes documented in these patients with hyperamylasemia included: surgery (thoracic and abdominal), renal failure, bowel infarction, trauma and pneumonia (Table II). In three of these 28 patients, no specific disease process could be identified.

TABLE III

SERUM AMYLASE ACTIVITY IN HYPOXEMIC PATIENTS WITHOUT CLINICAL PANCREATITIS

Case no.	Age	Sex	Diagnosis	Minimum pO_2 mm. Hg.	Maximum amylase I.U./l.
1	75	M	Myocardial infarction	66	1,350
2	25	F	Cervical fracture dislocation, pneumonia gastrointestinal bleeding	53	1,300
3	93	F	Cranial contusion, congestive heart failure	58	860
4	66	F	Myocardial infarction, Folate, B_{12} deficiency	48	115
5	72	F	Asthma, upper respiratory infection	52	228
6	64	F	Respiratory failure	36	70
7	29	F	Pulmonary embolus	49	105
8	67	M	Heart failure	55	162

Prospective study:—In order to determine whether the apparent association between hypoxemia and hyperamylasemia in the absence of clinical pancreatitis (Group 2) was more than a fortuitous occurrence, a preliminary prospective study was initiated. For entry into the study, the patient had to have sustained a period of significant hypoxemia (arterial $pO_2 < 75$ mm. Hg.). Patients with antecedent pancreatic disease were excluded, as were patients who showed any of the etiological factors associated with pancreatitis or renal failure. Only patients who fulfilled these requirements were accepted. The protocol called for amylase determinations to be made on all blood and urine samples ordered by the patient's physicians as part of management. It was hoped in this way, to monitor the relationship between pO_2 and serum amylase. The investigation was somewhat impaired by the fact that, for ethical reasons, arterial blood gas measurements or periodic venipunctures were not employed to monitor the serum amylase. Nevertheless, out of eight patients accepted into the study, three were found to have hyperamylasemia.

Our data to date are given in Table III. The case histories of two of these patients in whom amylase isoenzyme studies were carried out are summarized below.

CASE REPORTS

Case 1:—A 75-year old man presented to the RVH emergency clinic because of sudden onset of retrosternal "pressing" pain radiating to the neck and back. The patient felt nauseated, was sweaty and retched but did not vomit. Previous medical and surgical history were negative. He was a smoker, did not drink alcoholic beverages and took no medications. Physical examination revealed normal vital signs, decreased breath sounds, bilateral basal rales, jugular venous distention of 4-5 cm. and a II/VI systolic ejection murmur. Examinations of the salivary glands and the abdomen were entirely normal. Nasogastric aspiration yielded a small amount of "coffee ground-like" material which cleared and

TABLE IV

SUMMARY OF LABORATORY DATA, CASE 1

Day	pO_2 mm. Hg.	CPK (5-140) I.U./l.	SGOT (0-32) I.U./l.	Serum amylase (70-300) I.U./l.	Serum creatinine (1-1.8 mg./dl.)	Cam/Ccr (< 5.3%)
1	52*	1,301	219	346	–	–
2	–	573	96	1,350	1.5	3.2
3	–	332	55	350	1.3	5.6
4	79*	56	16	300	1.7	3.0

* Value corrected from room air patient was receiving 24% O_2.

did not recur. Stool examination for occult blood was negative. Admission pO_2 was 66 mm. Hg. on 24% O_2 (equivalent to 52 mm. Hg. if the patient was breathing room air) and serum amylase was 346 I.U./l. Chest x-ray revealed overinflated lungs with bilateral interstitial pulmonary edema. Electrocardiogram was consistent with left ventricular hypertrophy or inferior ischemia. The patient was treated with furosemide and responded dramatically; failure resolved immediately as did chest pain. The next day, BUN was 33; Cr, 1.5 mg./dl.; bilirubin (total), 0.4; alkaline phosphatase, 114; Ca^{++}, 9.5; WBC, 13,900 and hematocrit, 37.9%. Serum amylase was 1,350 I.U./l. with a pancreatic/salivary (P/S) amylase ratio of 0.30/0.70 I.U./l. (Normal P/S = .47/.53).*[12] Amylase clearance (Cam/Ccr) was 3.2% (normal < 5.3%).[13] On the basis of typical cardiac enzyme changes, the diagnosis of acute myocardial infarction was made. Serum amylase on the third day was 350 I.U./l. with a P/S ratio of 0.49/0.51 I.U./l. and Cam/Ccr of 5.6%. Upper gastrointestinal series revealed a small hiatus hernia with reflux and changes consistent with esophagitis. The patient was discharged on the 15th day. The relevant laboratory data are summarized in Table IV.

Case 2:—A 25-year old white woman, six weeks pregnant, sustained a fracture subluxation of the 7th cervical vertebrae after hitting her forehead on the dashboard during a vehicle accident. She experienced some pain in her arms and legs, then numbness and finally paraplegia but no loss of consciousness. Physical examination revealed tenderness on palpation of the cervical region, flaccid lower extremities with no voluntary contraction and decreased sensation from C_7 down. Examination of the abdomen was negative. Initial laboratory work-up was entirely within normal limits. Five days after admission, open reduction of the fractured vertebrae was performed, recovery being complicated by an inability to cough or swallow secretions. Three days postoperative, the patient became extremely dyspneic and was found to have pulmonary congestion confirmed by a portable chest x-ray. Arterial blood gases were measured and pO_2 was 53 mm. Hg. She was intubated and treated for pneumonia. On the fourth postoperative day, in the absence of abdominal pain or any objective physical findings, the nasogastric aspirate revealed coffee ground material and the hematocrit dropped from 41 to

* Derived from the following normal values; pancreatic isoamylase, 103 ± 31 I.U./l.; salivary isoamylase, 115 ± 31 I.U./l. (mean ± S.D.).

29%. This was attributed to stress ulcers, although gastroscopic or radiological confirmation could not be obtained. Treatment consisted of blood transfusions and antacids and there was no further bleeding. pO_2 continued low over the next seven days, at which point her case was brought to our attention. Examination at this time did not reveal evidence of salivary or pancreatic disease. A serum amylase determination the following day was 1,300 I.U./l. On the next day (the 13th postoperative day) amylase was 575 (P/S = .69/.31) and Cam/Ccr was 3.6%. A tracheostomy was performed. The following day amylase increased to 650 (P/S = .70/.30) and Cam/Ccr to 6.7%. Twelve days later, amylase had dropped to 420 and the Cam/Ccr to 3.8%, while the pO_2 and 73 mm. Hg. Serum amylase subsequently returned to normal values (220 I.U./l.).

Comment

The results of our retrospective study corroborate that a wide range of etiological factors may be associated with pancreatitis as well as with hyperamylasemia in the absence of clinical pancreatitis or salivary gland disease.[1-11] In the cases associated with clinical pancreatitis (Group 1), evidence of hypoxemia was found in 96% of the patients (26/27) in whom blood gases were analyzed. This may be somewhat misleading as blood gas measurements may have been ordered only in those patients with severe pancreatitis who are likely to have blood gas abnormalities. Correcting for the whole group, therefore, at least 46% of the 56 cases of pancreatitis seen in the hospital during the study period experienced an episode of hypoxemia (Table I). This compares favorably with the study of Ranson, Roses and Fink who found that arterial pO_2 fell below 75 mm. Hg. in 23/40 (58%) patients with pancreatitis.[14] It is generally accepted that hypoxemia in the presence of pancreatitis is a reflection of the severity of the pancreatitis rather than an etiological factor. The hypoxemia observed in nine of the 15 patients (60%) with hyperamylasemia in the absence of clinical pancreatitis or salivary gland disease, however, must have some other explanation. In our prospective study, of eight cases of acute hypoxemia without clinical pancreatic or salivary gland disease, hyperamylasemia occurred in three (38%).

A number of studies, conducted earlier by others provided convincing evidence that hyperamylasemia may occur in a number of clinical conditions associated with pulmonary pathology and/or hypoxia. Otsuki, et al[15] who studied 27 patients before and after open-heart surgery noted an increased amylase activity in 56% of the patients. The elevations of serum amylase activity, always of the salivary-type, were greater with a prolongation of extracorporeal circulation. In view of the earlier findings of this group that amylase of the salivary-type is present in normal and diseased lung tissue,[16] they suggested that amylase was released from lung tissue due to hypoxia during and after extracorporeal circulation. Unfortunately, no objective measurements of serum or tissue oxygenation were recorded in this study. A similar study carried out by Moores, et al[17] indicated that postoperative serum amylase activities were higher in patients subjected to continuous as opposed to pulsatile extracorporeal perfusion during open-heart surgery. In view of the fact that visceral circulation is improved using pulsatile perfusion, the authors suggested that pancreatic oxygenation was compromised during continuous flow perfusion. Although they implied that the amylase released was pancreatic in origin, no documentation of isoenzyme patterns was performed. Heffernon, et al[18] noted hyperamylasemia in 17 of 91 hospitalized heroin addicts. Thirteen of

these 17 patients were felt to be in acute respiratory distress, although blood gas determinations were not recorded. The authors suggested that the lungs were the source of the amylase released. An isolated case of salivary-type hyperamylasemia in a patient with bilateral pulmonary infiltrates suggesting a viral pneumonitis, is cited by Benjamin and Kenney.[19] There was no documentation of arterial blood gas levels.

A number of other studies provide additional indirect evidence linking hypoxemia and elevated serum amylase activity. Brandborg[2] states that hyperamylasemia has been found to occur after ruptured aortic aneurysm, while Jones, et al[20] reported that in cases of shock due to severe hemorrhage following ruptured aortic aneurysm, there was an apparent breakdown of zymogen granules in pancreatic acinar cells which contain amylase. In addition, Rogers[7] in a study of 1,000 patients with perforated peptic ulcer, found that patients who had experienced shock were more likely to have elevated values of serum amylase activity. Kelley's[9] report of a case of hyperamylasemia with ruptured ectopic pregnancy has been cited frequently in the literature. The patient described did not have any demonstrable pancreatic disease. On examining this case report, we note that at surgery the patient was found to have bled more than 2 liters into the peritoneal cavity. On the basis of our studies, we would raise the possibility that some of the diverse conditions which have been associated with hyperamylasemia, such as ruptured ectopic pregnancy and ruptured aortic aneurysm, may be explained by ischemic injury to the pancreas or salivary glands or other tissues forming amylase.

Hypoxemia may be a controlling factor causing the pancreas, salivary glands and other tissues such as lung to simultaneously increase their amylase output above normal limits. When one or the other is in some way additionally injured (by decreased available oxygen or blockage of ducts), an increase in the isoamylase from the structures reflects the additional trauma. In Case 1 of our prospective study, the prominent increase in serum salivery amylase may reflect salivary gland or pulmonary hypoxia. The salivary-type amylase released may have been related to venous stasis in the salivary glands due to jugular venous distention. The parotid glands, the primary serum salivary amylase source, are drained by the external jugular veins via the retromandibular veins. The submandibular glands, a lesser producer of salivary amylase, are drained by the internal jugular veins via the common facial veins.

It is also possible that the salivary-type amylase released was pulmonary in origin.[16, 18] In Case 2 of our prospective study, serum isoamylase quantification indicated a considerably greater amount of pancreatic type amylase. This would suggest that the major insult was to the pancreas. The high Cam/Ccr ratio noted at about the 14th postoperative day is consistent with this theory.[13]

There are a number of experimental studies which suggest that ischemic injury to the pancreas can lead to an increase in serum amylase activity. As early as 1862, Panum[21] showed in dogs that interference with pancreatic arterial blood flow resulted in morphological damage to the pancreas. That vascular disturbances alone, or in conjunction with ductal obstruction, could lead to a type of pancreatitis was confirmed in laboratory animals by Smyth,[22] Block,[23] Menguy[24] and Day.[25] It is well known that the vascular supply of the splanchnic viscera is severely compromised by hemorrhage, and the work of Forsyth[26] indicates that the pancreas may be the

organ most affected by the ischemia produced. He found, in monkeys, that with a hemorrhage of 50% of blood volume, blood flow to the pancreas decreased by 89%, whereas blood flow to the gastrointestinal tract and the liver decreased by only 56% and 23%, respectively.

In conclusion, the results of this and other recent studies[15, 17-19] suggest an association between hypoxemia and hyperamylasemia in the absence of overt disease of the pancreas or salivary glands. To the best of our knowledge this study is the first in which the presence of hypoxemia has been documented by arterial blood gas determinations. The limitations within which our studies were carried out do not permit us to be certain whether hypoxemia preceded and was the direct cause of the rise in serum amylase activity. In addition, the results of amylase isoenzyme studies in Cases 1 and 2 of our prospective study indicate that it is not possible to predict whether the source of the increased amylase activity is pancreatic, salivary or pulmonary in origin.[27] It is conceivable that in some cases, both salivary and pancreatic isoenzyme secretion are increased, thus preserving a normal P/S ratio. The validity of the hypothesis proposed requires validation by additional studies.

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Intra-arterial Tissue Adhesives for Medical Splenectomy in Dogs

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Transcatheter intra-arterial tissue adhesives are effective agents for producing medical splenectomy in dogs. Because of the rapid polymerization of the tissue adhesive, localized occlusion of the splenic artery mimicking a surgical ligation can be achieved leaving the intrasplenic vessels patent. Splenic infarction without evidence of infection was accomplished.

Introduction

A safe means of creating a medical splenectomy may be very desirable especially in poor surgical candidates who have thrombocytopenia on the basis of splenomegaly. Although previous attempts at medical splenectomy with transcatheter embolization of the splenic artery with gelfoam and blood clot has previously been reported with success in dogs[1, 2] it has met with failure in several human beings because of splenic abscess formation.[3, 4] Surgical ligation of the splenic artery on the other hand has been reported in both animals and humans to result in splenic infarction without the development of splenic abscess formation and with the reversal of hypersplenism in humans.[5] Because of this we were interested in investigating, in dogs, the usefulness of tissue adhesives in an attempt to perform a localized thrombosis of the splenic artery and create medically essen-

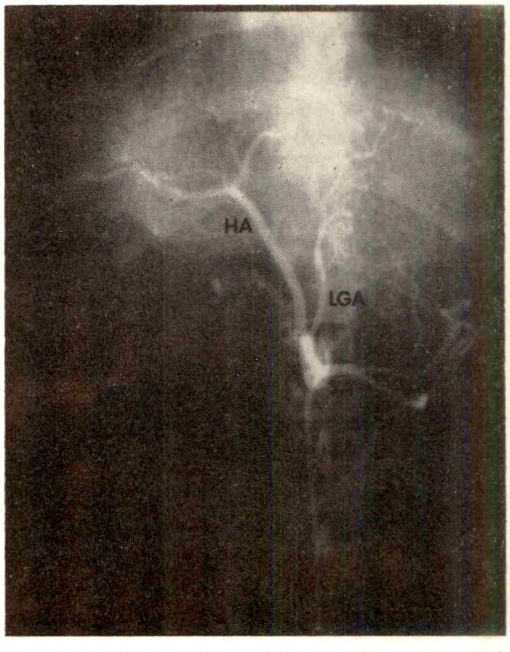


Fig. 1—Celiac artery angiogram prior to embolization. (HA-hepatic artery, LGA-left gastric artery, SA-splenic artery)

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Fig. 2—Tissue adhesive made opaque by mixing with tantalum powder is localized to proximal splenic artery.

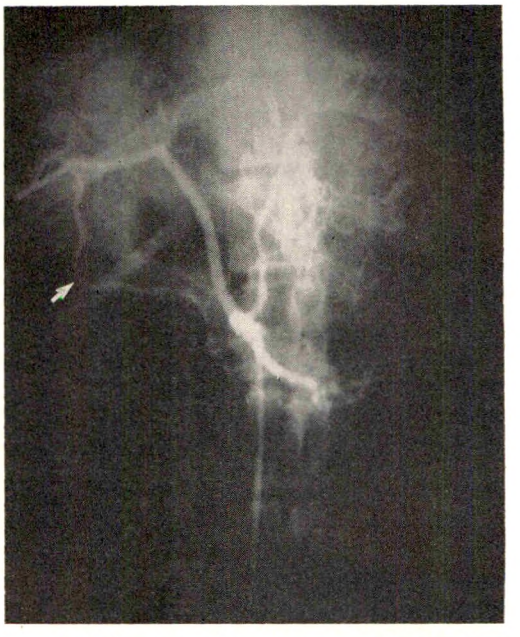


Fig. 3—Follow-up celiac artery angiogram three weeks following embolization demonstrating an obstructed splenic artery with collateral arterial supply (arrow) from the gastroduodenal artery to the region of the spleen.

tially a surgical ligation of that vessel. Because of the relative nonavailability of bucrylate,* another tissue adhesive flucrylate† was also utilized and the two agents were compared.

Materials and Methods

Transcatheter splenic artery occlusion with the use of tissue adhesives was performed in 11 mongrel dogs weighing 20.25-29.25 kg. Bucrylate was utilized in six dogs and flucrylate in five dogs. Under intravenous sodium pentobarbitol anesthesia, a cutdown was performed over the femoral artery. Selective catheterization was performed with an endhole 6.7 Fr. polyethylene catheter. A celiac artery angiogram was first performed (Fig. 1). The catheter was then advanced into the splenic artery. A safe position of the catheter for delivery of the tissue adhesive was determined by the lack of reflux of contrast agent back into the celiac axis or into the hepatic or left gastric arteries on a slow test injection of contrast agent. The occlusive agent bucrylate or flucrylate was then made opaque for embolization by taking 1 cc. of tissue adhesive and mixing it into a suspension with 2 gm. of tantalum powder:‡ In order to avoid premature polymerization of the tissue adhesive within the catheter great care was taken to keep the catheter and stopcock free of blood by careful flushing with sterile 5% dextrose and water. One and three tenths cubic centimeters of the tissue adhesive-tantalum powder mixture was then injected slowly under fluoroscopic control over two to three seconds. Since the

* Ethicon, Incorporated, Somerville, NJ.
† 3M Company, Saint Paul, MN.
‡ Fansteel Metals, North Chicago, IL.

TABLE I

NUMBER OF DOGS AND WEEKS AT TIME OF SACRIFICE

Bucrylate		Flucrylate	
Dogs	No. of weeks	Dogs	No. of weeks
1	2	2	3
1	4	1	4
2	7	1	7
2 Died anesthesia death		1 Died at 2 wk.	

catheter has a capacity of 1 cc., 0.3 cc. of the mixture was injected within the splenic artery (Fig. 2). Following embolization a catheter exchange was made and an immediate follow-up celiac angiogram was performed. A celiac angiogram (Fig. 3) was performed prior to sacrifice of the animals ranging from two to seven weeks (Table I) and a postmortem examination was obtained in all dogs.

RESULTS

The splenic artery was totally occluded in all dogs. In 10 dogs the occlusion was proximal (Figs. 1, 2 and 3) and in one dog the entire splenic artery proximally and distally was filled with tissue adhesive. This was caused by an overinjection of the embolic material. In two dogs, because of the rapid polymerization of the material within the catheter prior to its entry into the splenic artery, a catheter exchange was required with a second injection of tissue adhesives. In no animal was there evidence of reflux of material out of the splenic artery into the celiac, hepatic or left gastric arteries.

Follow-up angiograms prior to sacrifice demonstrated essentially no change in the appearance or extent of the intravascular occlusion but did reveal that collateral supply to the region of the spleen had developed in all dogs from the gastroduodenal branch of the hepatic artery (Fig. 3). Two dogs in which bucrylate had been injected died within the first 24 hours. This was attributed to anesthesia death since neither dog awoke from anesthesia and postmortem studies revealed no abnormalities. One dog injected with flucrylate died at two weeks. A blood count obtained in this dog at the initiation of the study revealed that it had marked leucocytosis and was, therefore, ill before the splenic artery was occluded.

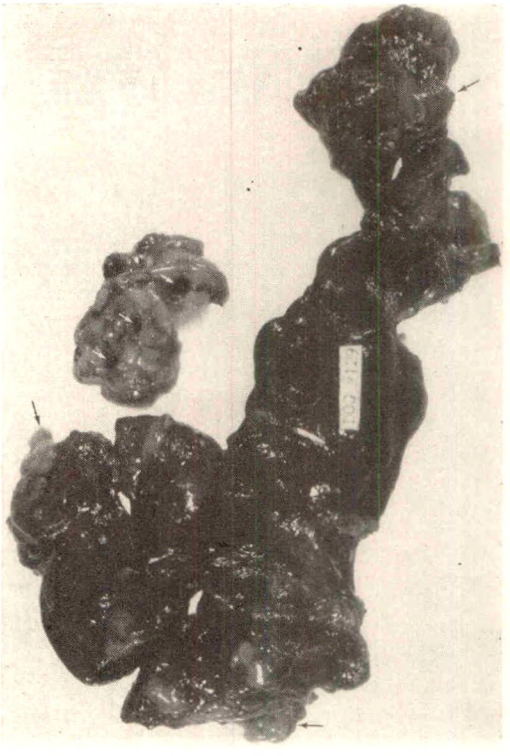


Fig. 4—Gross examination of the spleen three weeks following splenic artery occlusion shows multiple peripheral areas of infarction (white arrows), cross-section of splenic artery shows tissue adhesive-tantalum (black arrows) occluding the vessel.

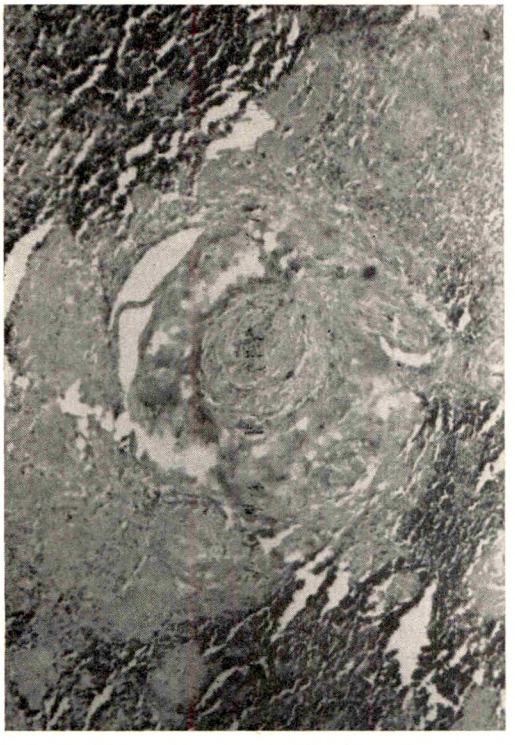


Fig. 5—Microscopic section of spleen shows area of necrosis without evidence of infection or of abscess formation. (Hemotoxylin and eosin, original magnification x100).



Fig 6—Experimental bucrylate occlusion of splenic artery in a dog. Cross-secion of splenic artery three weeks after occlusion shows an organizing thrombus of bucrylate, tantalum and clot. There is minimal tissue reaction (Hematoxylin and eosin, original magnification x100).

Koestner[6] estimates that the spleens in the dogs that we sacrificed should normally weigh between 150 and 400 gm. but the splenic weight in the animals that were autopsied at two weeks or later ranged between 60 and 96 gm. with a median weight of 83 gm. On gross examination the spleens demonstrated scattered areas of infarction (Fig. 4) that tended to be more peripheral in location. Microscopic sections of the spleen revealed the presence of scattered areas of necrosis (Fig. 5). In none of the spleens was there evidence of inflammatory reaction or of abscess formation. The main splenic artery revealed the presence of the adhesives and tantalum intermixed with partially organized blood clot. The arteries of the dogs injected with bucrylate revealed minimal tissue reaction involving the intima with only a minimal amount of fibrin deposition (Fig. 6). These are the findings that would be seen normally in the development of intravascular thrombosis. In the dogs injected with flucrylate, however, there was the presence of extensive tissue reaction within the splenic artery with destruction of all layers of its wall (Fig. 7). In addition, surrounding the blood vessel was a foreign body giant cell granulomatous reaction (Fig. 8).

Comment

Medical splenectomy with transcatheter embolization of the spleen with blood clot or gelfoam has previously been reported in dogs. These agents, however, produce temporary and distal intrasplenic

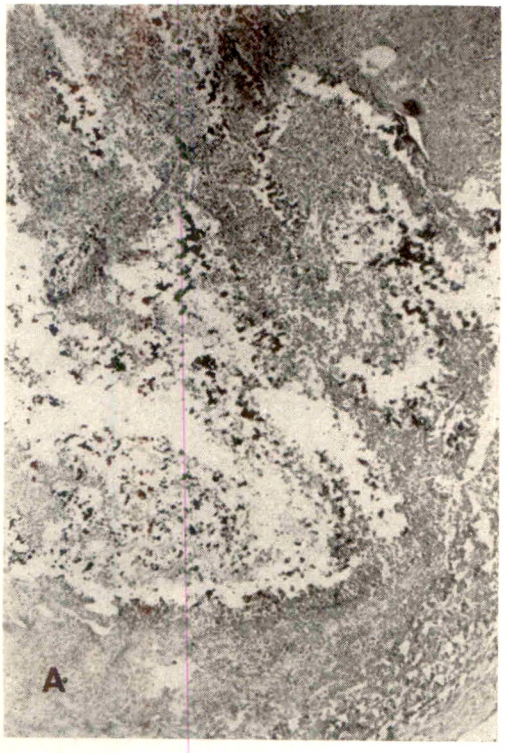


Fig. 7—Experimental flucrylate occlusion of splenic artery in a dog. Marked tissue reaction with necrosis of all layers of the artery (Hematoxylon and eosin, original magnification x25).

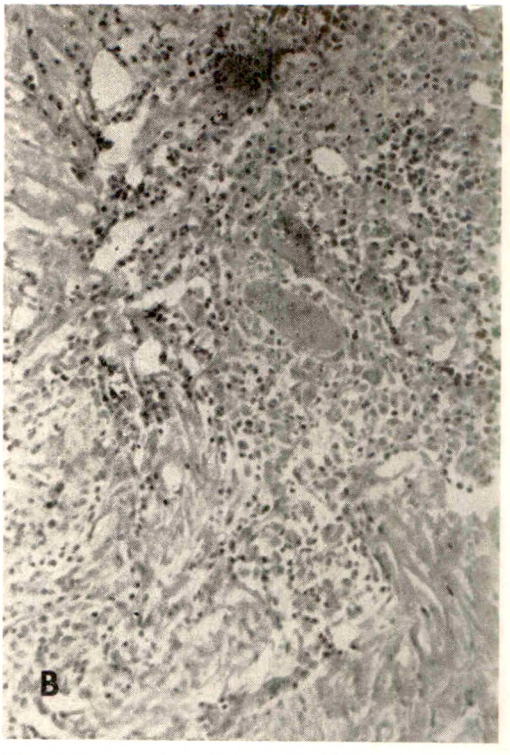
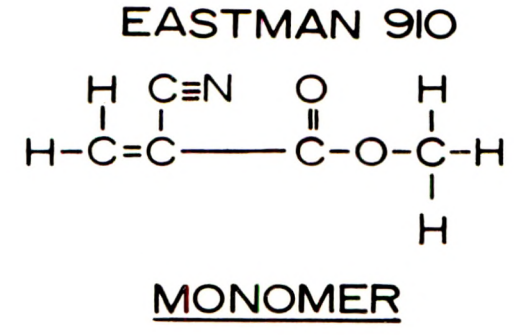


Fig. 8—Surrounding the artery is the presence of foreign body giant cell granulomatous reaction (Hematoxylin and eosin x250).

arterial occlusions.[1, 2] Although one human being is reported to have survived over a five-month period after splenic artery embolization by blood clot for the treatment of hypersplenism,[7] others have developed splenic abscess formation.[3, 4] In man the large size of splenic infarction which may lead to infection is likely related to the distal vessel embolization preventing subsequent development of collaterals to perfuse part of the infarcted area.

Surgical ligation of the splenic artery in animals and human being appears to be a safe technic. In animals it produces splenic infarction with a decrease in splenic mass and in select patients it has reversed hypersplenism.[8] Tissue adhesives offer another means of producing localized large vessel occlusion essentially mimicking a surgical ligation.[5, 9-10] In our experimental studies splenic artery occlusion was successfully produced and resulted in splenic infarction with decreased splenic mass without evidence of splenic infection or of splenic abscess development. It is thought that the developing collaterals prevent massive infarction and subsequent splenic infection. It is possible, however, that in the human being because of the development of collaterals splenomegaly may recur.

The tissue adhesives are a unique group of compounds. The first homologue was Eastman 910 or methyl 2-cyanoacrylate. This material as a monomer is a liqiud but as it undergoes anionic polymerization (Fig. 9) it solidifies. In blood this occurs within seconds. Eastman 910, however, is markedly histotoxic and may be carcinogenic in animals.[12] Because of this other



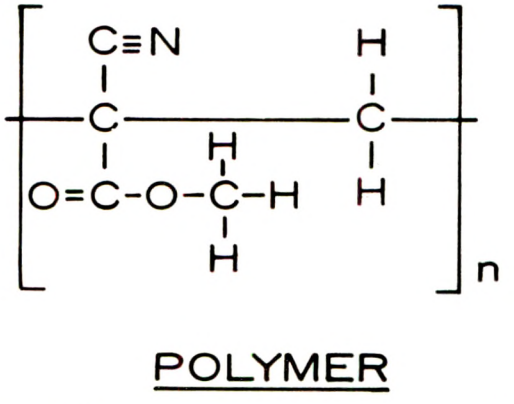


Fig. 9—Chemical structure of Eastman 910 (methyl 2-cyanoacrylate) monomer and polymer.

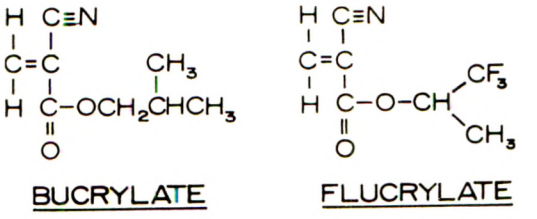


Fig. 10—Chemical structure of bucrylate (isobutyl ester of 2-cyanoacrylate) and flucrylate (trifluoroisopropyl ester of 2-cyanoacrylate).

tissue adhesives were developed. Bucrylate which is now relatively unavailable is an isobutyl ester of 2-cyanoacrylate and flucrylate is a trifluorinated isopropyl ester of 2-cyanoacrylate (Fig. 10). By increasing the number of carbon atoms on the ester part of the molecule the tissue histotoxicity is greatly reduced but there is a prolonged period of biodegradability.

Although we experienced no significant difference between the utilization of bucrylate and flucrylate it was noted that flucrylate produced extensive tissue histotoxicity when injected into the splenic artery in dogs. Prior to the use of flucrylate in humans this effect must be carefully evaluated by additional studies. The production, however, of limited inflammation in vessels may be a major advantage in specific situations when the development of collaterals adjacent to occluded vessels is undesirable. Bucrylate, on the other hand, shows only minimal evidence of tissue reaction. We have utilized bucrylate clinically in several patients with massive upper gastrointestinal bleeding[13] without evidence of significant side-effects attributable to its use. A great deal of experience, however, is required to safely utilize tissue adhesives in the clinical situation. One must always avoid contact of one's skin or eyes with the adhesive. The catheter prior to the injection of the material must be in a stable position within the vessel that is to be occluded. In order to prevent premature polymerization of the adhesive within the catheter the catheter is flushed with dextrose and water immediately prior to the injection of the agent. To obtain a carefully controlled injection under fluoroscopy it is important to make the tissue adhesive opaque and we have utilized tantalum powder. To avoid overinjection of the vessel with possibly reflux of the adhesive into other vessels a slow injection over several seconds is required. This also prevents distal embolization of the material into short gastric or small pancreatic vessels. Co-axial catheter systems and balloon catheters may also be used adjunctively to carefully control the injection of the tissue adhesive.

We have observed that when surgical ligation of the splenic artery accompanies

a distal splenorenal shunt (Warren shunt) there is always a rise of platelets and white blood cells. It has increased, however, the incidence of thrombosis of the newly constructed distal splenorenal shunt probably due to the release of clotting factors of splenic infarct. If transcatheter splenic artery occlusion is done well before surgery the suture lines of the newly constructed shunt are not flooded by tissue factors from the fresh splenic infarctions which promote clotting.

We have obtained permission from the Clinical Trial Committee of our institution for the use of tissue adhesives in creating a medical splenectomy and we expect to evaluate in select patients the efficacy and safety of this technic.

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Gastritis Polyposa in a Gastroenterostomy Anastomosis

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Review of the literature finds a strong point made for polyps of the stomach to be considered as "sentinels" of malignancy. The controversy over the transformation of gastric polyps into malignant tumors is coming to an end. Apparently, everyone agrees with a high incidence of malignant transformation in adenomatous polyps. The recent case report by Papp and Joseph of a hyperplastic polyp with malignant changes, seems to demonstrate that all polyps can undergo neoplastic transformation.

We believe that every gastrectomized patient should be gastroscoped once a year, even with an absence of symptoms or lack of x-ray findings. Any polyp, adenomatous or hyperplastic, should be removed endoscopically and studied histopathologically for possible association with or development of carcinoma.

Introduction

Multiple complications exist with any type of gastrectomy. Some complications are functional, for example, the "dumping syndrome", others are mechanical alterations at the level of the anastomosis. Strictures, peristomal ulcers, suture granulomas, prolapse of the mucosa and carcinoma are fairly frequent findings. An infrequent abnormality, however, is the polyp present in the anastomotic area with an absence of polyps in the rest of the stoma.

In the review of the literature, we found cases of polyps at the level of the anastomosis reported by Littler and Gleibermann,[1] Griffel, et al[2] and two cases by Drut and Velasco Vela.[3] Of these four cases, only one was a hyperplastic polyp;[3] the other three were cases of polypoid cystic gastritis.[1-3]

Case Report

J. B. is a 29-year old black man, admitted to the New Orleans Veterans Administration Hospital for work-up of iron deficiency anemia. Physical examination was irrelevant except for pale mucosa and mild tachycardia. Laboratory studies revealed hemoglobin of 8.1 gm; WBC, 5,200 and hematocrit of 25%. Occult blood in the stools varied at different times from trace to 2+. Even though the patient has had steady employment lifting crates and loading trucks, he retrospectively recognizes that in the previous 90 days, he had not been feeling well. He denies any history of melena, hematochezia, hematemesis, dizziness, fever or recent infection. Since his hemigastrectomy in 1971, the patient has had episodes of postprandial diarrhea and occasional epigastric discomfort, mainly after failing to adhere to his diet or taking alcohol in excess.

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Fig. 1—A "crown" of approximately 15 polyps at the level of the anastomosis.

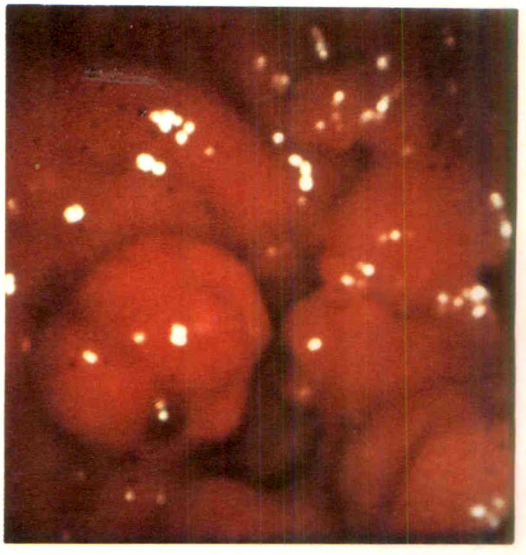


Fig. 2—The polyps varied in size from 0.3-1.7 cm. and some were pedunculated

A pertinent fact in his past history is his discharge from the army (Vietnam) due to an episode of hematemesis in 1969. He was treated for duodenal ulcer in an army hospital and discharged. After returning to New Orleans, he did not seek medical attention until July, 1971. At that time, he was seen at the New Orleans Veterans Administration Hospital with symptoms compatible with ulcer disease. The upper gastrointestinal series revealed a duodenal ulcer. Gastric analysis showed a fasting acidity of 9.69 mEq./l. with a pH of 2 and a Histalog stimulation of 102 mEq./l. He did well on medical treatment and improved until September, 1971. At that time he became symptomatic again and was treated medically for 15 days. On 21 September 1971, he underwent a Billroth II hemigastrectomy with bilateral truncal vagotomy. Except for occasional postprandial diarrhea, he did well and was followed when he made infrequent visits to the Gastroenterology Clinic, where he complained of "gas pain". In August, 1974, a gastroscopy revealed only peristomal gastritis.

During his 1976 admission, gastric analysis showed a pH of 7.1; upper gastrointestinal series revealed thick mucosal folds and adequate emptying of the stomach but no ulcer crater. Gastroscopy showed a normal esophagus with a small erythematous gastric stoma and a "crown" of approximately 15 polyps, at the level of the anastomosis (Fig. 1). The polyps varied in size from 0.3-1.7 cm. and some were pedunculated (Fig. 2). The largest polyp, 1.7 cm., (Fig. 3) had a blood clot that suggested it as being the source of the bleeding. Biopsies were obtained and reported as chronic gastritis. Endoscopic polypectomy was performed on three different occasions. The pathology report stated that these were hyperplastic polyps with no evidence of atypia. Four other smaller polyps were submitted and returned with similar pathological interpretation. There is no family history of polyps.

He responded well to iron therapy. The remaining polyps were removed at four subsequent endoscopies. Stools con-

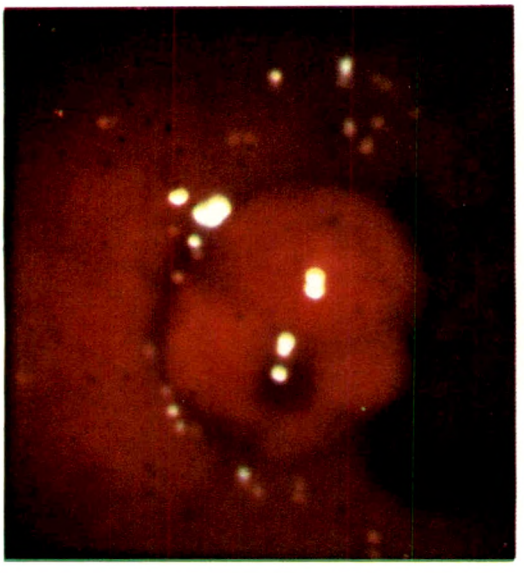


Fig. 3—A blood clot in the largest polyp suggested it as being the source of bleeding.

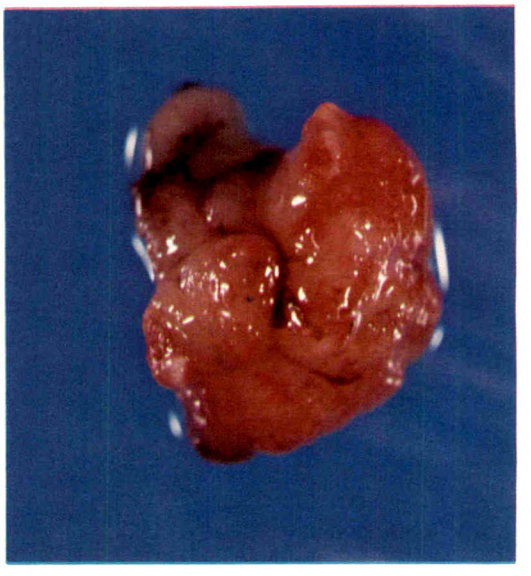


Fig. 4—The largest polyp, 1.7 cm., after polypectomy.

tinued to be trace to negative and his hemoglobin was stable. Air-contrast barium enema and colonoscopy were normal.

Comment

As previously mentioned, there are only four other reported cases of polyp lesions in the gastroenteric anastomosis. Three of those cases were of the cystic gastritis type, resembling colitis *cystica profunda*. Griffel, et al,[2] agreeing with Levine, et al,[4] postulated the possibility of a prolapse of the mucosa into the stoma with proliferation and cyst formation, as a cause for the cystic polyposis. Of those three cases, two had multiple polyps[2, 3] and one had a single polyp.[1] Our case had multiple hyperplastic polyps in the anastomotic area which is a totally different entity from the cystic type. The only similar case we found in the literature was one reported by Drut and Velasco Vela,[3] in which they found one 2.5 cm. hyperplastic polyp lesion in a patient that had undergone a Billroth II type of surgery, two years before. Noteworthy is the fact that both patients had Billroth II gastrectomies as did two of the three patients with cystic polyp lesions.[1, 3] The third patient had a partial distal gastrectomy and a gastroenterostomy.[2] Presently, there is a standing controversy as to the demonstration of the different types of gastric polyps and their relationship to carcinoma. In 1964, Ming and Goldman,[5] after examining 90 polyps from 49 patients classified them as "adenomatous polyps, regenerative polyps" and "polypoid carcinomas". The "adenomatous" type, 21% of the cases, resembled the adenomatous polyps of the colon. They were large, over 2 cm., located in the antral region, mostly and had marked intestinal metaplasia and atypism. The "regenerative polyps", 76% of the cases, were smaller in size and randomly located in the stomach and the intestinal metaplasia, if present, was focal or mild (16 out of 76 polyps). The incidence of association with carcinoma was similar in both types of polyps, while neoplastic or malignant transformations were not demonstrated in their studies.

In 1961, Tomasulo[6] reviewed 97 cases of gastric polyps. He divided these into "adenomatous polyps" and "hyperplastic polyps" stating that 76% of his cases were hyperplastic polyps. *He reported that 59% of the adenomatous polyps and 28% of the hyperplastic polyps were associated with carcinoma.* Marked atypical cells were only found in the adenomatous polyps. Carcinoma *in situ* was reported by this author in five of 23 cases of adenomatous polyps, none in hyperplastic polyps. In 1972, Goldman and Appleman[7] published a larger study on 133 polyps from 44 patients and proposed a different classification. They suggested the elimination of the term "adenomatous" which would be replaced by the generic name "gastric mucosal polyp" because all have, basically, the same histologic component. They also proposed classifying them, with or without atypical hyperplasia, in a new group called "antral-foveolar polyps", which are always benign.

There seems to be agreement on several aspects of the above three studies. First of all, *the authors agree that atypia is the most important factor in determining the possibility of malignant transformation.* They also agree that polyps over 2 cm. in size and those located in the antrum are more likely to be malignant. Another area of agreement is that polyps should be considered a "sentinel" of possible hidden malignancy, either in the gastrointestinal tract or elsewhere. No matter what type of polyp, the distribution of malignant association is fairly even in all the cases they studied.

Summary

Our case presents some singular characteristics that require scrutiny. The patient had multiple "hyperplastic polyps", from 0.3-1.7 cm. in size. The location of the polyps in this case cannot be used as a prognostic sign due to the previous surgery. The size of 1.7 cm., the largest polyp, (Fig. 4) is very close to the 2 cm. limit, suggested by Ming, et al,[5] Tomasulo, et al[6] and Goldman, et al.[7] The hyperplastic polyp, found by Drut and Velasco Vela,[3] was 2.5 cm. in size and contained cells with dysplastic nuclei and poorly differentiated characteristics that make one wonder if this "hyperplastic polyp" was undergoing malignization. Several questions come to mind. Do these polyps in the perianastomotic area, where the pH is alkaline, behave in the same manner as all of the gastric polyps, previously described? Does the frequency of carcinoma, discovered in patients who had previous gastrectomies, indicate that the polyps were present prior to the carcinoma but not diagnosed due to lack of symptoms or lack of evidence in an x-ray examination? Since polyps occur so frequently in patients who had Billroth II gastrectomies, does it suggest that the type of surgery had something to do with the appearance of these neoplasms? In a recent publication Papp and Joseph[8] reported a hyperplastic polyp, 2.5 cm. in size, with adenocarcinoma transformation.

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Communication from Abroad

Hemolysis During Salicylazosulfapyridine Therapy

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In 36 unselected patients with ulcerative colitis or Crohn's disease taking 4.5-6 gm. salicylazosulfapyridine per day the incidence of hemolysis and its relation to the serum level of salicylazosulfapyridine (Salazopyrin®, Azulfidline®, SASP), free sulfapyridine (SP) and acetyl sulfapyridine (ac-SP) was investigated. In 19 patients hemolysis was present. Serum levels of free SP were significantly higher in these patients ($P < 0.001$). All patients with a serum SP level higher than 37 μg./ml. had hemolysis as compared to only four of 21 patients with a serum SP level below 37 μg./ml. Four patients had evidence of hemolytic anemia. In these patients the serum SP level was higher than 55 μg./ml. Eighteen of the 19 patients with hemolysis were slow acetylators while six of the 17 patients without hemolysis belonged to the slow acetylator phenotype.

Introduction

Salicylazosulfapyridine (SASP) is extensively used in the treatment of inflammatory bowel disease. The drug is often administered in a large dose over a long period.

Only a small proportion of the ingested SASP is absorbed in the small bowel. The major step in the SASP metabolism is the reductive cleavage of the azo-link by colonic bacteria releasing 5-aminosalicylic acid (5-ASA) and sulfapyridine (SP). The latter is absorbed almost completely from the colon and excreted in the urine, partly after acetylation and/or glucuronidation while the 5-ASA moiety is largely excreted in the feces.[1-3] Adverse reactions to SASP such as abdominal discomfort, nausea, headache and malaise have been related to the serum level of SP.[4, 5]

It is well known that sulfonamides, particularly sulfanilamide and SP may cause oxidative hemolysis of the erythrocytes.[6] As early as 1940 Moeschlin[7] described seven patients with frank hemolysis associated with the use of SP. The erythrocytes of some of these patients contained inclusion bodies (Heinz-bodies). Hemolytic anemia during SASP therapy has been described by some authors[4, 8-10] but the incidence seems to be low. Miller, et

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al,[11] however, described mild hemolysis without anemia in 28% of the patients taking 2-8 gm. SASP per day. The aim of the present study was to investigate the incidence of hemolysis during SASP maintenance therapy and to see whether there was a correlation between hemolysis and the serum level of SASP, SP and acetyl-SP (ac-SP).

Patients and Methods

Thirty-six unselected patients with ulcerative colitis or Crohn's disease taking 4.5-6 gm. SASP per day were studied. Eleven patients were seen as in-patients and 25 as out-patients. The four patients who developed hemolytic anemia were taking 6 gm. SASP for two to five weeks. In the other patients this period varied from two weeks to more than one year. There were 17 males and 19 females aged 14-65 years (mean 32.9 years). Four patients had undergone an ileocecal resection. None of them had undergone a total or partial colectomy. None of the patients received other drugs that may cause hemolysis. In all patients liver and renal functions were normal. The serum levels of SASP, SP and 5-ASA were determined by the methods of Sandberg and Hansson.[12-14] The analytic error of these methods was found to be not more than 5%. The serum levels of SP-glucuronide and ac-SP-glucuronide are generally low (less than 5 μg./ml. and were for that reason not determined in all patients. The same applies to 5-ASA that after acetylation in the liver is rapidly excreted in the urine resulting in serum levels less than 2 μg./ml. The acetylator phenotype was determined by the method of Evans.[15]

The serum haptoglobin level, a sensitive indicator of hemolysis[16-18] was determined by radial immunodiffusion; normal value 1.8 ± 0.4 gm./l. (mean ± SD). In many patients with Crohn's disease or ulcerative colitis, however, the serum haptoglobin level is increased due to the chronic inflammation. A serum haptoglobin level lower than 0.8 gm./l. was considered indicative for hemolysis.

Hemoglobin was estimated according to the cyanhemoglobin method;[19] normal value, 12.5-16 gm./dl. Lactate dehydrogenase (LDH) was estimated by the method of Wroblewski and La Due.[20] In healthy persons LDH levels were always lower than 175 U./l. Reticulocytes and Heinz-bodies were stained with brilliant cresyl blue. Glucose-6-phosphate-dehydrogenase (G6PD) levels of the erythrocytes were not estimated because a deficiency of this enzyme is extremely rare in the population native to the Netherlands. The results were analyzed using the Student "t" test.

Results

Out of 36 patients 19 showed evidence of hemolysis (serum haptoglobin level below 0.8 gm./l.). In 10 patients serum haptoglobin was not detectable at all.

The serum level of free SP was significantly higher in patients with hemolysis (Table I). There was no correlation between the serum haptoglobin level and the serum concentrations of SASP or of ac-SP. All patients with a serum level of free SP more than 37 μg./ml. showed evidence of hemolysis as compared to only four of 21 patients with a serum level of free SP below 37 μg./ml. Other parameters indicating hemolysis such as reticulocyte index and serum LDH also showed a correlation with the serum haptoglobin level (Table I). The mean hemoglobin level did not differ significantly in the two groups of patients. Four patients, however, had evidence of hemolytic anemia. These patients were slow acetylators. The serum level of free SP in these patients was higher than 55 μg./ml. After reduction or temporary ces-

TABLE 1

RESULTS (MEAN ± SD) RELATED TO THE PRESENCE OF HEMOLYSIS IN 36 PATIENTS WITH CROHN'S DISEASE OR ULCERATIVE COLITIS TAKING 4.5-6 GM. SALICYLAZOSULFAPYRIDINE PER DAY

	Hemolysis present	Hemolysis absent	
	Serum haptoglobin < 0.8 gm./l. (mean 0.19 gm./l. range 0-0.77 gm./l.)	Serum haptoglobin > 0.8 gm./l. (mean 2.33 gm./l. range 0.99-4.36 gm./l.)	P value
No. of patients	19	17	
Hemoglobin (gm./dl.)	12.3 ± 1.9	13.1 ± 1.3	NS
Reticulocytes (%)	5.7 ± 4.3	2.6 ± 2.2	< 0.02
LDH (U./l.)	195.0 ± 38.8	141.3 ± 38.0	< 0.001
Serum level of SASP (μg./ml.)	13.2 ± 13.6	11.2 ± 11.2	NS
Serum level of free SP (μg./ml.)	53.8 ± 24.5	15.9 ± 12.3	< 0.001
Serum level of ac-SP (μg./ml.)	6.0 ± 4.1	5.9 ± 5.0	NS
Serum level of SP + ac-SP (μg./ml.)	59.8 ± 25.1	21.8 ± 14.3	< 0.001
Acetylator phenotype: fast	1	11	
slow	18	6	

sation of the SASP dosage the symptoms of hemolysis disappeared and in the patients with hemolytic anemia the mean hemoglobin level rose from 10.4-12.8 gm./dl. Heinz-bodies in the red cells were found in seven patients (in 1-4% of the erythrocytes). There was no correlation between serum SP level and the occurrence of Heinz-bodies. The mean serum level of free SP in patients without Heinz-bodies was 40 μg./ml. (range: 0-98 μg./ml.) In patients with Heinz-bodies the mean serum level was 43 μg./ml. (range: 7.9-93.2 μg./ml.).

COMMENT

Thanks to the experiments of Schröder and Campbell[3] and Peppercorn and Goldman[1, 2] the knowledge of the SASP metabolism has increased considerably. Pharmacokinetic studies demonstrated that after the splitting of SASP, SP is absorbed almost completely from the colon. Therefore the serum SP concentration can reach rather high levels. Studies of Schröder and Evans[5] and Das, et al[4] strengthened the presumption that most of the side-effects during SASP therapy are related to high serum concentrations of total SP (more than 50 μg./ml.).

Hemolytic anemia associated with the use of SASP was first reported by Spriggs, et al.[10] They found frank hemolysis in two of 32 patients receiving SASP. Dick, et al[9] observed hemolytic anemia in only one of 40 patients taking 4-6 gm. SASP per day. During the period 1966-1970 five patients with hemolytic anemia caused by SASP

have been reported to the Swedish Adverse Drug Reaction Committee.[8] Das, et al[4] described hemolytic anemia in five of 133 patients taking 1.5-8 gm. SASP per day. The total serum SP concentration in these patients was greater than 42.5 μg./ml. All five of these patients were slow acetylators. Apart from the report of Miller, et al[11] already mentioned, there are no studies about the incidence of hemolysis without anemia during SASP therapy.

The results of our study show that there is a high incidence of hemolysis during ingestion of 4.5-6 gm. SASP per day (in 53% of the patients) and that this hemolysis is related to the serum level of free SP. In most cases hemolysis is compensated for by an increased erythropoiesis but especially in patients with a serum level of free SP over 55 μg./ml. there is a serious risk of hemolytic anemia.

The serum level of free SP depends, apart from the dosage of SASP, mainly on the acetylation rate of SP in the liver. Serum SP levels are considerably higher in slow acetylators (about 60% of the West-European population) than in fast acetylators.[4, 5] Table I shows that 18 out of 19 patients with hemolysis were slow acetylators whereas only six out of 17 patients without hemolysis were slow acetylators.

The incidence of hemolysis in our group of patients is higher than described in earlier reports. One of the explanations may be that patients with increased red cell destruction but without anemia, are not investigated for signs of hemolysis. On the other hand in patients with ulcerative colitis or Crohn's disease anemia is often ascribed to blood loss in the feces or chronic inflammation. Finally it should be noted that our study was limited to patients taking a high maintenance dose of SASP (4.5-6 gm. per day).

To a certain extent our findings agree with those of Pounder, et al.[21] They found contracted red cells in 23 of 50 patients receiving a mean dose of 2.5 gm. SASP per day as maintenance therapy for ulcerative colitis. The results suggested that the observed red cell contraction was associated with mild hemolysis. The patients with contracted red cells had a significantly higher serum total SP level than those with undamaged red cells.

This study shows that determination of the acetylator phenotype is important in patients receiving a high dose of SASP because the majority of slow acetylators taking 4.5-6 gm. SASP per day will reach serum levels of free SP that cause hemolysis. Especially in patients with serum levels of free SP over 55 μg./ml. hemolytic anemia frequently occurs.

Hemolysis should therefore be considered in any patient with Crohn's disease or ulcerative colitis taking SASP where loss of blood in the feces or chronic inflammation fails to account for the anemia.

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The Role of Total Parenteral Nutrition in the Treatment of Inflammatory Bowel Disease

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Indications for the use of total parenteral nutrition (TPN) in the treatment of inflammatory bowel disease include improvement of nutrition in the pre- and postoperative periods, management of gastrointestinal fistulas and as an adjunct to medical therapy. In general, patients with Crohn's disease respond better than those with ulcerative colitis. TPN is supportive and does not lead to a long-lasting cure in most cases.

Over the past decade, total parenteral nutrition (TPN) has been increasingly used as therapy for a variety of gastrointestinal diseases.[1-7] The patient is provided daily requirements of fluids, electrolytes and vitamins and sufficient calories and protein for positive nitrogen balance via infusion of these essential nutrients through a large central vein.

This technic is expensive, time-consuming for both the patient and medical staff and occasionally accompanied by serious mechanical, infectious and/or metabolic complications.[3-5, 7] Thus, a brief assessment of the role of TPN in the treatment of inflammatory bowel disease seems timely and prudent.

Currently, there are three broad indications for TPN in the management of patients with ulcerative colitis or Crohn's disease e.g., 1. pre- and postoperative care; 2. gastrointestinal fistulas and 3. as an adjunct to primary medical therapy.

Pre- and Postoperative Care

Patients with inflammatory bowel disease may fail to respond to medical therapy and require surgery. Often, because of chronic diarrhea, malabsorption, poor caloric intake, fever and extracolonic complications, they are quite malnourished and in negative nitrogen balance.

TPN rests the bowel, improves nutrition and restores positive nitrogen balance, thereby improving the patient's status as a surgical candidate.[5, 7-9] Postoperatively, it may be used if oral intake is delayed, or during the early period of metabolic adaptation in the short bowel syndrome.

Gastrointestinal Fistulas

During the course of Crohn's disease, 20-30% of patients will develop gastrointestinal fistulas.[10, 11] Based on animal studies which have shown a marked decrease in fistula output and protein loss when TPN was utilized,[12] various surgeons have tested this technic in humans.

In 1973 Dudrick's group[13] reported on 62 patients with 78 fistulas seen over a two-year peroid and managed with TPN. Twenty-two, or about one-third of the group, had Crohn's disease. The over all rate of nonsurgical closure was 70.5% and an additional 22% were cured by later surgery. The mortality was 6.5%, much less than in their pre-TPN experience. The average length of time for the fistulas to close after the onset of TPN was approximately 27 days.

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Two additional papers published in 1974 show good but less impressive results. In treating 38 patients (about one-third had inflammatory bowel disease) with TPN, Aguirre, et al[14] found 30% to show healing of the fistulas. The length of treatment ranged from 40-48 days. The over-all success rate, including those eventually requiring surgery was 70.5% and mortality equalled 20%. The authors noted that if fistulas were complicated by obstruction. abscess, or lack of bowel continuity, spontaneous closure was not likely to occur with TPN alone.

Eisenberg, et al [9] noted a 28% nonsurgical closure rate in 18 patients, all with Crohn's disease. The remainder required surgery with an eventual two year success rate of 90%.

Cohen, et al[15] mention two children with ileocolitis who showed complete healing of fistulas when treated with TPN. Anderson and Boyce,[16] to the contrary, noted no long-lasting improvement in two adults with advanced Crohn's disease and fistulas.

In summary, then, one can expect decreased fistula output and improved nutrition in patients with gastrointestinal fisulas treated with TPN. Initially, surgery can be avoided in perhaps 30-70% and even if needed later, the over all success rate for closure is higher than in the past, at 70-90%.

Primary Therapy

Since the first report of TPN in the management of patients with inflammatory bowel disease appeared eight years ago,[1] considerable experience has accumulated and been published. Such patients have been chronically and seriously ill and usually represent failure of medical therapy including adrenocortical steroids.

In 1973 Anderson and Boyce[16] reported their experience with TPN in eight adults with advanced Crohn's disease. The length of treatment averaged 30 days and all noted decreased diarrhea, an increased sense of well-being, and weight gain. Three showed signs of improvement on sequential radiographic studies. Follow-up, however, showed remissions to last usually less than three months and the initial improvement was felt to basically be a transitory one.

Two papers have appeared from the Massachusetts General Hospital—the first in 1973[17] and then again in 1976.[18] Their very ill patients were divided into several categories. Nine patients with Crohn's disease of the small bowel were treated with TPN an average of 29 days. Six did not require surgery and one was weaned from steroids. Another 14 had Crohn's disease of the small and large bowel or of the large bowel alone. TPN allowed eight to avoid later surgery. In sum, then, 14 of 23 patients avoided surgery being followed an additional 42 months. TPN did not prevent surgery in ten of 11 patients with ulcerative colitis. Moreover, when this group of colitis patients was compared to an earlier one not treated with TPN, there was no significant difference in general outcome.

In the discussion following one of these papers,[17] Fitts briefly mentions that 85% of his 70 patients with Crohn's disease and 50% of 30 patients with ulcerative colitis had shown "remission" with TPN.

The group at the Cleveland Clinic[9] reported on 46 extremely ill patients with Crohn's disease given TPN. Nine received it as primary therapy and all "did well".

Vogel, et al[19] used TPN for treatment of an acute episode of Crohn's disease in eight patients with extensive small bowel

disease. All initially improved and steroids were decreased in seven. Over the next four months to three years, however, only four remained in remission.

Dean, et al[20] treated 16 patients with inflammatory bowel disease over a one year period. Almost half (7/16) did not require later surgery but no follow-up data are given.

Dudrick, et al[21] have recently reported their experience with TPN in 52 patients with Crohn's enterocolitis. Twenty-eight, or over half, did very well, 13 initially responded but later required surgery and 11 were unable to avoid more immediate surgery.

Sotgin, et al,[22] from Italy, felt TPN helped one of two patients with ileitis. Of five patients followed with ulcerative colitis, four initially responded. Follow-up ranging from three to 14 months showed three to still be in remission.

Cohen, et al[15] found TPN not to help one child with ulcerative colitis. Of five children or adolescents with Crohn's disease, two had a remission lasting six and eight months, two showed only partial clinical improvement, and one was a failure.

Another use for TPN as an adjunct to medical therapy is in preventing or reversing growth arrest in adolescents chronically ill with Crohn's disease.[23] Four such cases of growth failure were helped with TPN given for up to six weeks. All showed additional weight gain and improved nutrition. Of interest is the fact that three nonetheless required surgery one to 16 months later.

Finally, patients with extensive Crohn's disease may receive TPN as outpatient therapy. Jeejeebhoy, et al[24] have used it in three patients and noted clinical improvements and active social lives. Fleming, et al[25] studied seven patients with home TPN over an average period of 17 months. Although complications other than malnutrition were not prevented, there was a decrease in number of hospitalizations and improved nutrition in all.

In sum, TPN may be very helpful in the management of critically ill patients with inflammatory bowel disease—Crohn's disease more so than ulcerative colitis. It is supportive and not curative in most cases. One can expect approximately 50% of those with Crohn's disease to show an initial remission but long-lasting relief and avoidance of later surgery is uncommon.

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Clinical Vignette

Phlegmonous Esophagitis Associated with Epiphrenic Diverticulum

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Diverticula of the distal esophagus (epiphrenic diverticula) are relatively rare but more often cause symptoms compared to the traction diverticula of midesophagus. They are generally large and their orifice is about 4-6 cm. above the lower esophageal sphincter;[1] they generally produce esophageal obstructive and regurgitative symptoms and are associated with esophageal motility disorder; they have been described in association with hiatus hernia, esophageal carcinoma and eventration of the diaphragm.[2] Association of suppurative (phlegmonous) esophagitis with epiphrenic diverticula is not common. We report a case of phlegmonous esophagitis associated with a large epiphrenic diverticulum; phlegmonous esophagitis was diagnosed by fiberoptic endoscopy and biopsy and it responded to antibiotic therapy.

Case Report

A 62-year old white man was admitted with a one and a half-year history of dysphagia and regurgitation. Dysphagia was worse with hot solids as compared to cold liquids. In the three weeks before admission he developed odynophagia and lower retrosternal pain. During the previous year he lost 10 kg. and had become progressively weak. He had a chronic cough with yellow expectoration for many months but recently the cough and expectoration increased and the color of the expectoration became yellowish green. During the month prior to admission he de-

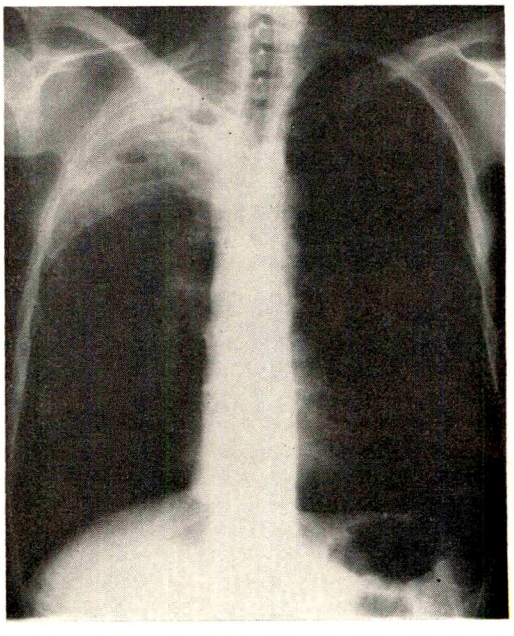


Fig. 1—Chest roentgenogram showing abscess in right upper lung.

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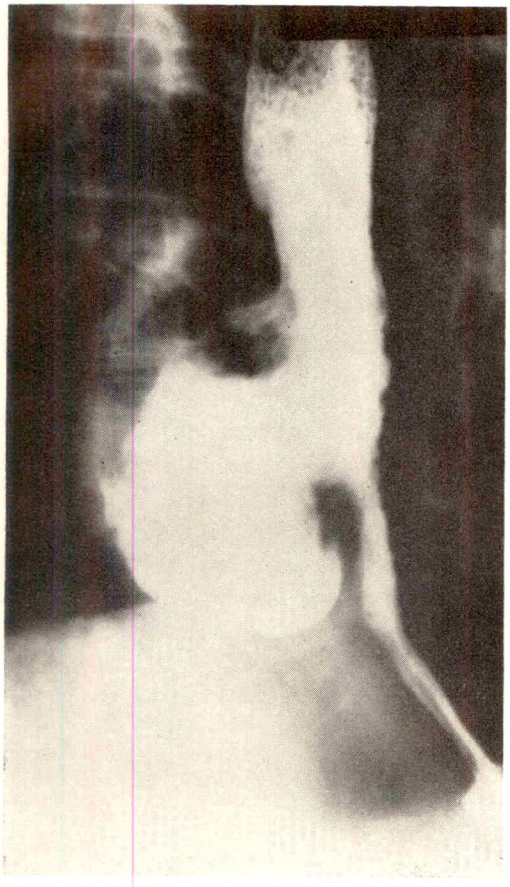


Fig. 2—Esophagogram showing epiphrenic diverticulum.

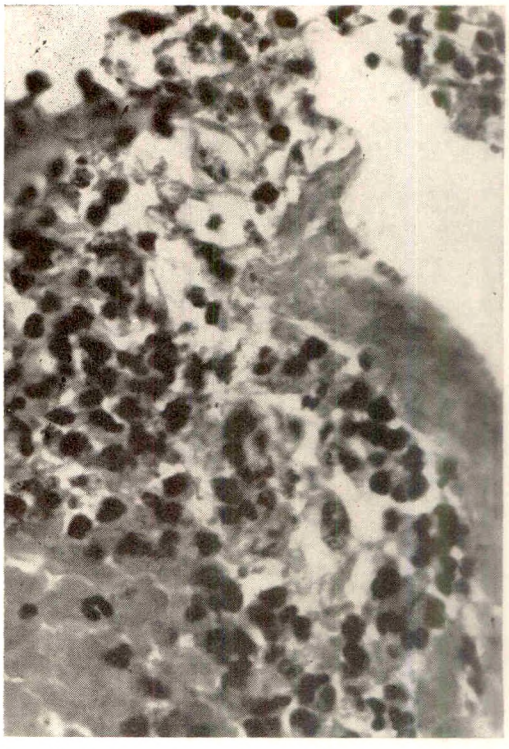


Fig. 3—Endoscopic esophageal biopsy showing infiltration of the esophageal wall with acute and chronic inflammatory cells (Hematoxylin and eosin, original magnification x250).

veloped right-sided pleuritic chest pain. There was no history of alcoholism in the preceding seven years but before that he admitted to heavy alcohol intake. He smoked three packs of cigarettes a day for 20 years. On examination he was cachetic and febrile. There was dullness to percussion and breath sounds were decreased in the right upper chest. There was marked digital clubbing. Hemoglobin was 8.8 and hematocrit 26.9. Total white count was 18,200 with 80% polys. Arterial blood gases showed pH 7.54, pCO_2 35 and pO_2 67. Sputum smear showed mixed flora. Chest roentgenogram (Fig. 1) showed multiple small abscesses in the right upper lobe; the left lung was clear. P.P.D. and candida skin tests were negative. Sputum for AFB, stool guaiac and blood cultures were negative. Fiberoptic bronchoscopy showed no sign of malignancy; bronchial washings and biopsy showed acute and chronic inflammatory changes. Upper gastrointestinal series showed a large (6 cm. × 5 cm.) esophageal diverticulum (Fig. 2) at the junction of middle and lower third of the esophagus. No abnormality of esophageal motility was seen on roentgenogram; stomach and duodenal bulb were normal. Fiberoptic panendoscopy[3] showed the opening of the diverticulum at 23 cm. Food residue could be seen in the diverticulum. In the region of the diverticular opening, there were necrotic ulcers covered with extensive purulent exudate. Biopsy was taken from the

edge of the ulcers. At the time of biopsy purluent, foul smelling material escaped from the base of the ulcer. Stomach, duodenal bulb and post bulbar regions were normal. Histologic examination of the biopsy (Fig. 3) showed infiltration of the esophageal wall with acute and chronic inflammatory cells and colonies of bacteria were seen in the wall of the esophagus. The patient was treated with clindamycin 300 mg. every six hours orally for two weeks. Repeat chest roentgenogram after four weeks showed marked improvement in the lung, clearing of the abscesses and residual pleural thickening. His dysphagia markedly improved although symptoms of esophageal regurgitation persisted. A repeat endoscopy showed complete healing of the suppurative ulcers. Since his pulmonary problems were secondary to esophageal regurgitation, surgical treatment of the esophageal diverticulum was recommended but the patient refused surgery.

Comment

There is no agreement regarding the exact length of the epiphrenic segment of esophagus; it has been defined as the distal 4 cm., the distal 10 cm. or the distal one-third.[4-5] These diverticula generally become large;[6] in the present case the diverticulum measured 6 cm. × 5 cm. Sometimes the diverticulum has a long and narrow neck and such diverticula retain barium and food for long periods. These are often associated with esophageal motor abnormally such as achalasia or diffuse esophageal spasm[1, 7] but sometimes they occur in the absence of obvious motor dysfunction. Although motility studies were not done, there was no evidence of achalasia or tertiary contractions on roentgenogram in this patient.

Patients with small epiphrenic diverticula are generally asymptomatic. Patients with large diverticula generally complain of nocturnal regurgitation or regurgitation of undigested food. Such nocturnal regurgitation may be responsible for chronic pulmonary problems including lung abscess as was seen in the present case. Substernal fullness and pain may be due to distention of the sac; sometimes the pain may resemble angina.[8]

The symptoms of dysphagia and odynophagia are generally not due to the diverticulum itself but probably are secondary to associated esophageal disease. In the present case odynophagia was probably due to phlegmonous esophagitis because the pain disappeared after the patient was treated with clindamycin which was given for the treatment of lung abscess. The repeat endoscopy showed healing of the suppurative ulcers. Phlegmonous esophagitis was probably due to stasis and chronic infection in the sac. Cases of carcinoma[9] developing in the epiphrenic diverticulum have been reported and a relationship to chronic stasis has been postulated.[6] The entity of phlegmonous gastritis is well described[10] and the predisposing factors seem to be chronic gastritis, alcoholism, hypoacidity, low socioeconomic status and chronic malnutrition. Phlegmonous esophagitis is not common and in the present case presence of necrotic food material might have been the predisposing factor.

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Clinical Vignette

Choledochal Cyst Presenting as Acute Pancreatitis

Evaluation with Endoscopic Retrograde Cholangiopancreatography

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A unusual case of choledochal cyst in an adult presenting as acute pancreatitis is described. Subsequent evaluation by ERCP revealed two atypical features, involvement of the cystic duct (proximal dilatation) and a long (six times normal) intrapancreatic common channel, which may be etiologically related to the pancreatitis.

Introduction

Choledochal cyst uncommonly presents in adult patients (20 years of age or older) and even more uncommonly presents as acute pancreatitis. We are aware of only three such case reports[1-3] in the English literature. We have recently seen such an instance and have shown, using endoscopic retrograde cholangiopancreatography (ERCP), an anomalous duct union only recently appreciated which may explain the development of acute pancreatitis in this setting.

Case Report

B. A., a 20-year old Guatamalan female, was admitted to Los Angeles County-University of Southern California Medical Center with a 24-hour history of right upper quadrant pain which radiated to the right flank and back. There was associated emesis but no fever, jaundice or pruritus. She denied alcohol or drug abuse, use of birth control pills, abdominal trauma or family history of pancreatitis or gallbladder disease. She had been hospitalized on one occasion 19 months previously with similar complaints, but the pain had subsided without specific therapy. On that admission her physical examination was normal with the exception of a temperature of 36.5° C and tenderness in the right flank and upper quadrant. The laboratory data are noted in Table I.

Physical examination on the current admission included a temperature of 36.5° C, no icterus, moderate tenderness in the right upper quadrant and flank with no masses or organomegaly. Laboratory data are noted in Table I. Chest x-ray was normal and a supine x-ray of the abdomen revealed a nonspecific ileus pattern with no calcifications. The clinical impression was that of acute pancreatitis. In the absence of any other etiology for the pancreatitis and suspecting choledocholithiasis, an

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TABLE I

LABORATORY VALUES RELATED TO HOSPITAL ADMISSIONS

	Albumin/ globulin gm./dl.	Bilirubin total/direct mg./dl.	BLB units alkaline phosphatase	K units SGOT/ SGPT	Percent of control prothrombin time	Amylase/ diastase U./dl.	WBC no./cu.mm.	Calcium mg./dl.
5/75 (First admission)	4.3/3.1	0.6/0.1	2.1	25/15	100	60/200	9,000	9.0
12/76 (Second admission)	3.9/3.2	1.2/0.6	1.6	20/5	90	900/18,000	11,000	8.6

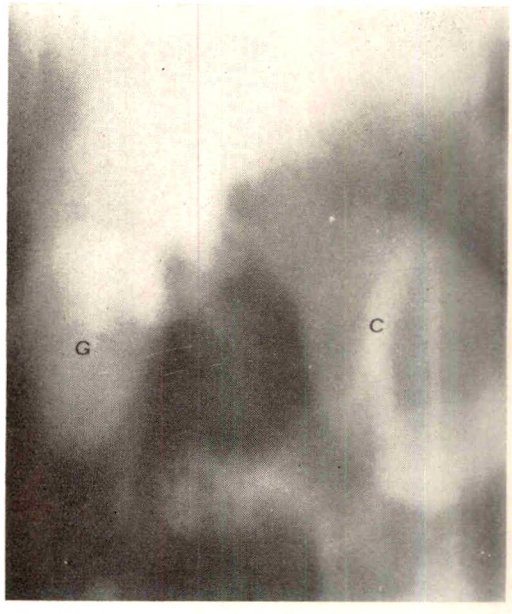


Fig. 1—Intravenous cholangiogram: Tomogram shows gallbladder (G) laterally and choledochal cyst (C) medially.

ultrasound study was then performed and revealed a cystic mass in the right upper quadrant most consistent with a choledochal cyst but did not exclude the possibility of a pseudocyst. No stones were identified. Shortly thereafter, an intravenous cholangiogram was performed (Fig. 1) and demonstrated a 4.8 × 6.7 cm. dilatation of the common bile duct without evidence of stones. The gallbladder was normal. The terminal portion of the common bile duct was not seen clearly. An upper gastrointestinal series showed mucosal edema of the second portion of the duodenum but no evidence of an extrinsic mass.

During the next 48 hours, the patient's temperature rose to 39.5° C and her WBC count rose to 19,400 /cu.mm. Abdominal examination revealed rigidity, guarding and increased tenderness in the right upper quadrant with diminished bowel sounds of normal pitch. Amylase/creatinine clearance ratio was 10%. The patient was started on ampicillin and genta-

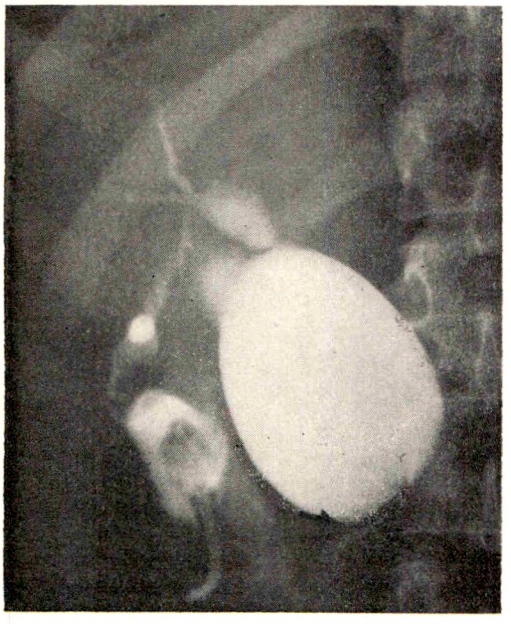


Fig. 2—Postoperative cholangiogram via cholecystostomy tube. The cyst has been opacified and shows dilatation involving cystic duct. Ducts with Y-shaped configuration distal to cyst initially thought to be bifid common bile duct. Later ERCP showed this to be duct of Wirsung (single arrow) and common bile duct (double arrows).

mycin but subsequent blood cultures were negative. In the face of these developments perforated viscus was considered possible and an exploratory laparotomy was performed. Findings included a normal gallbladder, a Type I choledochal cyst and interstitial pancreatitis with areas of inflammation and fat necrosis in the right paracolic gutter. Ascitic fluid amylase was 16,000 U./100 ml. and gallbladder bile amylase was greater than 20,000 U./100 ml. Aerobic and anaerobic cultures of the gallbladder bile showed no growth. Cholecystostomy was performed and by the fifth postoperative day the amylase and diastase had returned to normal.

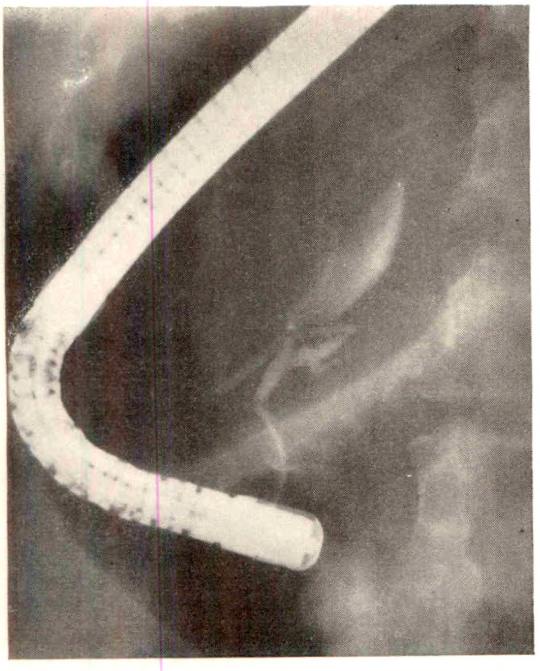
A postoperative cholangiogram by cholecystostomy tube (Fig. 2), prior to discharge confirmed the choledochal cyst and showed that the dilatation also extended into the cystic duct. The examination also outlined two ducts with a Y-shaped configuration distal to the cyst which was thought to represent bifid common bile duct.

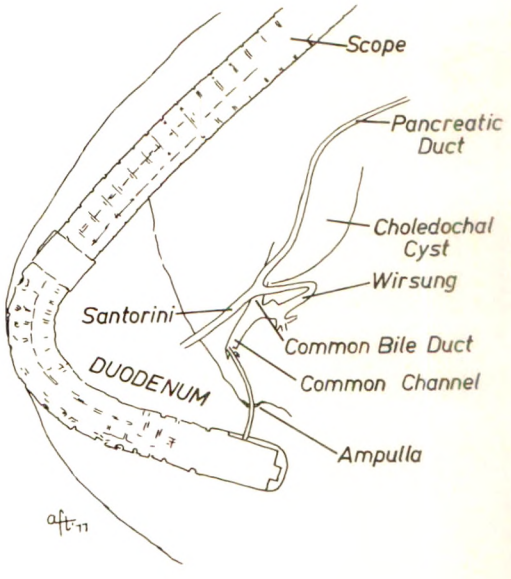
During a two-month follow-up period the patient remained symptom-free with normal serum amylase and urinary diastase values. Subseqeunt determinations of cholesterol and triglyceride were 243 and 82 mg.% respectively.

Nine and one-half weeks after operation an ERCP outlined the previously demonstrated choledochal cyst together with an anomaly of the duct of Wirsung. An unusually long common channel, 2.8 cm. in length (normal 0.2-1.0 cm; average 0.46 cm.),[4] was shown (Fig. 3), representing the vertical limb of the previously demonstrated Y-configuration (Fig. 2). The lateral limb of the Y was now seen to be the common bile duct distal to the cyst and the medial limb was the duct of Wirsung. This latter duct was outlined by contrast medium which had refluxed from the biliary tract during the postoperative examination via the cholecystostomy tube (Fig. 2). Figure 4 demonstrates the completely opacified cyst and gallbladder and a short segment of narrowing at the junction of the cyst and common hepatic duct.

Comment

The complications of choledochal cyst are serious and include cholangitis, hepatic abscess, biliary cirrhosis, portal vein thrombosis and rupture of the cyst with consequent peritonitis. Although previously noted, the association with acute pancreatitis as occurred in our patient appears to be a rare occurrence and its etiology is unclear. Suggested factors have included gallstones, common-duct stenosis with biliary reflux and stasis and compression with obstruction to the pancreatic duct by the

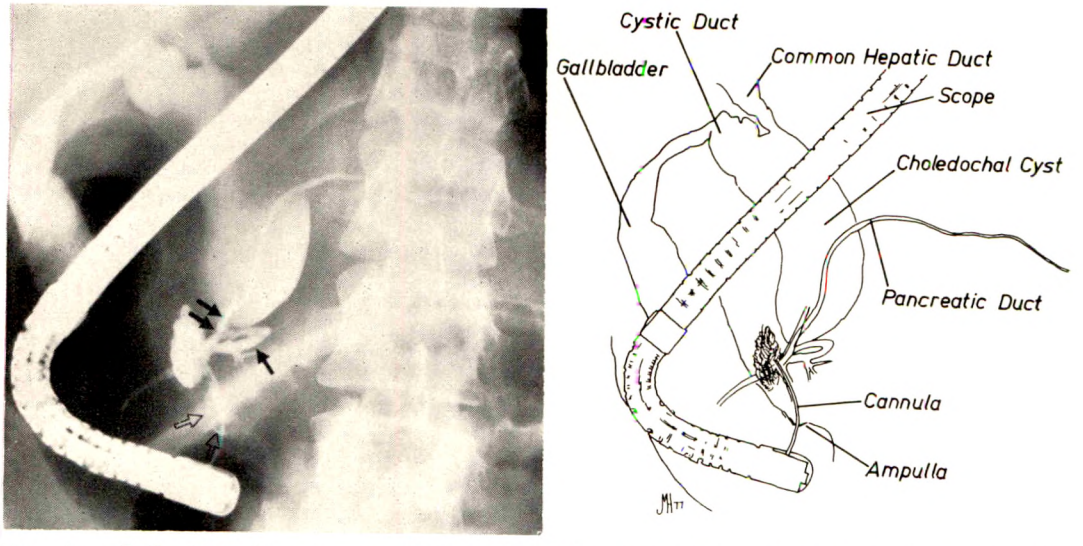




Figs. 3a and 3b—Early film showing long common channel 2.8 cm, short common duct distal to cyst, and duct of Wirsung.

choledochal cyst or by associated pancreatic duct stricture. McWhorter's case description in 1939 is the only one which described intrapancreatic duct pathology[5]. Thirteen years after hepaticoduodenostomy for relief of obstruction produced by a choledochal cyst, the patient was necropsied and found to have pancreatic cysts, calculi and chronic pancreatitis. The patient had diabetes mellitus and hypertension but no known bouts of acute pancreatitis. Thomas, et al described one of the first cases in the English literature to be studied with ERCP.[6] Their patient had bouts of cryptic abdominal pain but no pancreatitis and was found to have an intrapancreatic choledochal cyst with a normal pancreatic duct. In separate papers Jansen and Stephens[7] and Pauline[8] described teenage patients who presented with acute pancreatitis and were found to have choledochoceles (Type III) and gallstones were also present in the patient described by Jansen. Kotner and McFadden[3] described a further instance of pancreatitis in which a choledochal cyst contained three gallstones. Karjoo, et al[9] and Cuschieri and Davies[2] stressed the recurrent nature of pancreatitis which may accompany choledochal cyst. Kimura, et al[4] described 16 patients studied by ERCP and emphasized the frequency of demonstrating an anomalous union of common bile duct and pancreatic ducts. The average length of the terminal common duct was six times normal. None of the cases were reported to have pancreatitis.

Pancreatitis was unequivocally established in our patient during her second admission to the hospital. Although chemical evidence of pancreatitis was not present at her first admission nineteen months previously, the similarity of her symptoms at that time and the lack of any other explanation suggest that her initial episode of pain was



Figs. 4a and 4b—Later films showing filled choledochal cyst, dilated proximal cystic duct and gallbladder. Duct of Wirsung (single arrow) and common bile duct (double arrows). Note short segment of narrowing at junction of common hepatic duct and choledochal cyst. Ampulla of Vater (open arrows).

in some way related to her choledochal cyst and may well have been due to pancreatitis. ERCP was performed nine and one-half weeks after resolution of the acute pancreatitis and revealed no evidence of pancreatic duct stricture or gallstones. The two remarkable anatomical abnormalities observed, however, were dilatation of the proximal portion of the cystic duct and, perhaps of more importance in the context of pancreatitis, a very long intrapancreatic course of the common channel produced by the joining of pancreatic duct with common bile duct. These abnormalities have very recently been remarked upon[4] and indicate that anomaly of the normal anatomy in choledochal cyst may not always be confined to the extra pancreatic biliary passages but may also include those within the pancreas. Furthermore, such anomalies may explain the occasional occurrence of pancreatitis in this setting. In our case the length of the common channel was 2.8 cm. which is similar to that described in this anomaly by others[4] and six times that found normally.

The essential features of choledochal cyst are well reviewed in recent articles.[10, 11] Alonso-Lej, et al[12] defined three major types: Concentric or fusiform dilatation of the common bile dut (I), diverticulum of the common bile duct (II) and choledochocele (III): over 90% of cases are of Type I. Type I cysts usually are limited proximally at about the level of the cystic duct and commonly terminate at a stenotic segment in the distal common duct. The gallbladder and cystic duct are normal.

In the present instance, the combination of features appears to indicate a variation of the Type I choledochal cyst not previously delineated.

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Clinical Vignette

Carcinoma of the Small Intestine in Regional Enteritis

Presentation of a Case and Review of the Literature

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A case of carcinoma of the jejunum occurring in a patient with Crohn's disease of 30-years' duration is presented. Forty-seven previously reported small bowel carcinomas in Crohn's disease patients are reviewed.

The incidence of small bowel carcinomas in patients with Crohn's disease has been cited as being as low as 0.08%, a figure which is still higher than the 1 in 10^9 population which would be predicted if the two diseases were independent of one another. The average age of incidence of the Crohn's carcinomas was 46.5 years while that for the *de novo* group was 55 years. The sexual ratios were 2.46:1 and 2:1, males to females, for the respective groups. The *de novo* carcinomas had a slight predilection for the duodenum at 40.7% while the latter group had a heavy predilection for the ileum at 70.8% and contained no duodenal carcinomas. The prognosis of the Crohn's group appeared to be much worse than that of the *de novo* group with five-year survivals of 3.7% and 20-22% respectively. Late diagnosis in the enteritis group was felt to be the major reason for this. Finally, several pathological differences between the lesions in both groups are presented.

The first case of adenocarcinoma of the small intestine in a patient with regional enteritis was described by Ginzburg, et al in 1956.[1] Since this report, approximately 50 cases of the coincidence of these two diseases have been described. This relatively small number when compared to the number of patients with regional enteritis has prompted some to say that the coincidence of these two diseases is only a matter of chance. Several factors exist, however, to indicate that the coincidence of these problems is not by chance alone.

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Case Report

Case EB 10145. The patient is a 53-year old white male admitted to the Midtown Hospital of the New York University Medical Center with a 32-year history of regional enteritis. His chief complaint on this admission was two weeks of episodic bilious emesis occurring several hours after ingestion of solid food. In 1946, he had undergone an exploratory laparotomy at the Mount Sinai Hospital in New York. He was told that the diffuseness of his disease made relief by surgery impossible. Biopsy of an enlarged mesenteric lymph node re-

vealed granulomas. Over the ensuing years, his disease was characterized by periodic diarrhea, largely controlled by dietary restriction as well as antispasmodic and antidiarrheal drugs. In 1965 and 1970, he developed episodes of multiarticular arthritis, both of which were treated successfully with his only courses of steroids.

Upon admission, the patient was slightly dehydrated. He had hypoactive bowel sounds. Abdominal x-rays were not indicative of bowel obstruction. He was maintained NPO and on intravenous fluids for several days. A clear fluid diet was begun and an upper gastrointestinal series with small bowel follow-through was obtained. The barium study revealed diffuse enteritis with some dilation of the proximal jejunum. Barium reached the colon within four hours but some remained in the proximal jejunum as late as 48 hours. Abdominal x-rays continued to show no signs of obstruction. Despite treatment with intravenous fluids, a nasogastric tube, rectal cathartics and steroids (hydrocortisone 200 mg./day), he soon could not tolerate even clear fluids without vomiting.

The patient was, therefore, taken to the operating room. Laparotomy revealed complete obstruction of the jejunum approximately 30 cm. from the ligament of Treitz by a mass involving the wall of the bowel. An area approximately 45 cm. from this point was partially obstructed by a similar mass. An appropriate small bowel resection was performed. Final pathological examination revealed the area of complete obstruction to be caused by an adenocarcinoma with a small mucosal origin in an area of regional enteritis. The more distal obstruction was caused by a metastatic serosal implant.

The patient's postoperative recovery was uneventful and he was discharged on 12.5 mg. of prednisone per day.

He was readmitted with anastomotic obstruction six months later. Laparotomy and enteroenterostomy were performed. Diffuse metastases were noted. Chemotherapy was begun but the patient expired seven months after his initial operation.

Previously Reported Cases

Forty-seven cases of carcinoma of the small bowel arising in an area previously involved with regional enteritis have heretofore been described (Table I). The average age of these patients is 46.5 years. The oldest patient described is 80 years old;[2] the youngest patient described is 21 years old.[3] Thirty-two males and 13 females are included among the patients, for a male to female ratio of 2.46:1. The sex of three of the patients was not available.[4, 5] Eight cases were described as being jejunal. Thirty-four cases arose in the ileum. The precise location in the six remaining cases was not available. Thus, at least 70.8% of these carcinomas arose in the ileum and 16.6% arose in the jejunum. No carcinomas in patients with regional enteritis have arisen in the duodenum.

Most of the patients in the present review were documented as having regional enteritis many years prior to the discovery of the carcinomas. Other patients admitted to having bowel complaints for many years. The average duration of symptoms prior to the diagnosis of carcinoma was 17.1 years with the shortest period being three months and the longest period being 45 years.[6, 7]

One of the treatment modalities utilized in regional enteritis, especially during the first two decades following the description of this disease, was exploratory laparotomy with construction of a by-pass to exclude the involved segment of bowel. It is interesting to note that 13 or 27% of the herein discussed small bowel carci-

TABLE I

Authors	Age of pt.	Sex of pt.	Site of tumor	Length of time of regional enteritis prior to onset of cancer	By-pass
Almond, et al [23]	48	F	Ileum	2.5 yr.	No
Beachley, et al[24]	51	M	Ileum	20 yr.	No
Beachley, et al[24]	51	F	Ileum	25 yr.	No
Berman and Prior[25]	51	M	Ileum	25 yr.	No
Bersack, et al[18]	26	M	Diffuse	11 yr.	No
Brown, et al[26]	55	F	Ileum	25 yr.	Yes
Bruni, et al[27]	51	M	Ileum	29 yr.	No
Bruni, et al[27]	60	M	Ileum	16 yr.	Yes
Buchanan, et al[28]	47	M	Ileum	29 yr.	No
Cantwell, et al[29]	60	M	Ileum	31 yr.	No
Clemmensen and Johansen[30]	70	M	Diffuse	14 yr.	No
Darke, et al[6]	60	M	Ileum	45 yr.	No
Farmer, et al[31]	43	M	Jejunum	9 yr.	Yes
Farmer, et al[31]	61	F	Jejunum	7 yr.	No
Fielding ,et al[12]	24	M	Jejunoileal	8 yr.	No
Fleming and Pollock[8]	55	F	Ileum	13 mo.	No
Floch and Slattery	53	M	Jejunum	32 yr.	No
Frank and Shorey[32]	48	M	Ileum	13 yr.	Yes
Frank and Shorey[32]	55	F	Ileum	12 yr.	Yes
Ginzburg, et al[1]	30	M	Jejunum	19 yr.	No
Goldman, et al [3]	21	F	Jejunum	10 yr.	No
Greenstein and Janowitz[2]	80	M	Ileum	40 yr.	Yes
Hoffert, et al[33]	40	M	Ileum	21 yr.	No
Kornfeld, et al[34]	36	F	Jejunum	8 yr.	No
Lear[4]	—	—	Ileum		No
Lightdale, et al[17]	56	M	Ileum	23 yr.	No
Lightdale, et al[17]	53	M	Ileum	25 yr.	No

TABLE I

Authors	Age of pt.	Sex of pt.	Site of tumor	Length of time of regional enteritis prior to onset of cancer	By-pass
Lightdale, et al[17]	49	M	Ileum	15 yr.	No
Magnes and Debell[35]	71	M	Ileum	15 yr.	No
Marshak[5]	—	—	—	—	
Marshak[5]	—	—	—	—	
Morowitz, et al[36]	41	M	Ileum	22 yr.	No
Newman, et al[10]	67	M	Ileum	20 yr.	No
Papp and Pollard[37]	39	M	? Primary	21 yr.	No
Rha, et al[7]	38	M	Ileum	3 mo.	No
Saeed, et al[16]	47	M	Ileum	20 yr.	No
Savage, et al[9]	36	M	Ileum	8 yr.	No
Schofield[38]	Mid 20s	M	Ileum	7 yr.	No
Schofield[38]	Mid 20s	M	Ileum	4 yr. p By-pass	Yes
Schuman[39]	35	M	Ileum	29 yr.	Yes
Sheil, et al[40]	40	F	Ileum	5 yr.	No
Steele and McNeely[41]	38	M	Ileum	10 yr.	Yes
Tyers, et al[21]	32	M	Jejunum	12 yr.	Yes
Weingarten, et al[42]	44	F	Jejunum	28 yr.	Yes
Weingarten and Weiss[43]	28	F	Ileum	5 yr.	Yes
Wyatt[44]	33	M	Ileum	7 yr.	No
Zisk, et al[45]	61	F	Ileum	Not documented	No
Zisk, et al[45]	62	F	Ileum	23 yr.	Yes

nomas have occurred in previously by-passed segments.

Several pathological considerations are of interest in these cases. First is the so-called "invisibility" of the lesion. In 17 or 52% of the 33 cases reviewed by Fleming and Pollock, the diagnosis of carcinoma was suspected neither by the surgeon nor the pathologist who examined the specimen, as all of the gross abnormalities present were compatible with regional enteritis

alone.[8] This raises serious questions about areas of gross regional enteritis left behind at laparotomy. Another question which is raised is whether or not the incidence of carcinoma in this disease would be found to be higher with more thorough examination of Crohn's disease material from operations and autopsies. Another interesting finding discussed by Fleming and Pollock is that of "dysplasia", a possible intermediary stage between inflamed mucosa and carcinoma, which was found adjacent to the carcinoma in 27% of their reviewed cases.[8] Finally, these authors discuss a peculiar type of invasion in which discrete acini appear to invade through the bowel wall in a manner similar to that of endometriosis. This was found in 38.5% of the cases they reviewed.[8]

Other authors have also noted interesting pathological findings in this group of carcinomas. Savage, et al reviewed 27 cases in which 10 or 37% showed predominance of a so-called mucin-retaining or "signet ring cell".[9] In 1975, Newman, et al reported a case in which a carcinoma, arising in an area of Crohn's disease, was found to be surrounded by an area of intraepithelial neoplasia. Both the tumor and the surrounding area contained a tumor-associated surface antigen which was reactive with an antiserum prepared against a carcinoma of the colon.[10]

Comment

In 1955, Hughes described a case of reticulum cell sarcoma which arose in a patient who had been diagnosed 14 years earlier as having Crohn's disease. The malignancy arose in an area near the anastomosis which had been done at the time of diagnosis prompting the author to consider that the involved bowel had undergone malignant degeneration.[11] In 1972, Fielding, et al described a series of 295 patients with Crohn's disease in which they felt that gastrointestinal malignancy was more frequent than would be expected in a normal population. Pancreatic and small intestinal malignancies were very statistically significant in this study.[12] Dihman and Toker described an enteroblastoma occurring in a patient with Crohn's disease in 1973.[13] Also in 1973, Weedon, et al presented a follow-up study of 499 patients of the Mayo Clinic with Crohn's enteritis, enterocolitis and colitis. Utilizing a life table comparison, they concluded that the incidence of colon cancer was approximately 20 times greater among their patients than in a normal population. These cancers tended to occur in younger people than colorectal cancers in patients without Crohn's disease and the carcinomas in the study patients tended to be on the right side of the colon.[14]

In 1956, Ginzburg, et al described the first adenocarcinoma of the small intestine occurring in a patient with regional enteritis.[1] Including the present report, 48 such cases have now been described. Several authors have felt that there is more than a chance association. The incidence of spontaneously occurring carcinomas of the small bowel is estimated at 0.3/100,000 population per year.[6] In a combined series of 127,174 autopsies, the incidence of small bowel carcinoma was 0.098%.[15] Carcinoma occurring in a case of regional enteritis has been reported in 0.08%.[16] When one considers the chance of both diseases occurring in the same patient, however, the incidence seems higher than chance. The incidence of Crohn's disease has been variously described as 9, 25, 27, 32.5/100,000 population and increasing. [17] Darke, et al, ultilizing these data, estimated the likelihood of both diseases occurring in the same individual to be 1 in 10^9 population if these diseases were independent of one another. In their series of 1,062 cases of Crohn's disease, the incidence of small bowel malig-

nancy was 1 case/354 enteritis patients, thus suggesting an association.[6]

Several other areas of comparison between small bowel carcinomas arising in Crohn's disease and those arising spontaneously warrant consideration. First, regarding location, 16.6% of the Crohn's disease carcinomas arose in the jejunum while 70.8% were ileal. None were found in the duodenum. Three cases were not described as to precise location and three cases were described as being diffuse with the exact site of the primary not being identified.[4, 5, 18] This distribution parallels that of Crohn's disease. In a large combined series of *de novo* small bowel carcinomas, 40.7% were found in the duodenum, 34.8% were found in the jejunum and 24.5% were found in the ileum.[16] The fact that 27% of the Crohn's disease carcinomas occurred in by-passed segments is probably just a reiteration of the predilection of these carcinomas for the ileum. The average age of incidence for the group with Crohn's disease is 46.5 years while that of the *de novo* group is 55 years.[16] The sexual predilection for males is somewhat comparable at 2.46:1 for the Crohn's disease group and 2:1 for spontaneously occurring carcinomas. The prognosis of spontaneously occurring carcinoma shows a five-year survival of 20-22% with an average length of survival of 30 months.[16] Follow-up in the group with previously diagnosed Crohn's disease is quite incomplete but average survival has been estimated at 6.5 months with a five-year survival of 3.7%.[16] Perhaps the reason for this discrepancy lies in the tendency for diagnosis and treatment in the latter group to be undertaken later. The reason for this is likely to be that some of the symptoms of small bowel tumors such as malaise, weight loss, low-grade bleeding, diarrhea and symptoms of partial obstruction are also symptoms of regional enteritis which are frequently treated non-operatively.[19, 20] This situation prompted Tyers et al to suggest operation in any patient with severe symptoms of Crohn's disease after a symptom-free period of four or more years.[21]

Several pathological features of the Crohn's carcinomas are worthy of reiteration and comparison with the *de novo* cases. These include the "endometrial pattern of invasion" which has apparently not yet been described in *de novo* carcinomas and the frequent presence of intermediate cells between the mitotic and inflammatory areas in the Crohn's group.[8] Spontaneously occurring small bowel carcinomas are typically described as being fairly well differentiated lesions which are frequently mucus-secreting.[22] This provides a contrast to the poorly differentiated "signet ring cells"[9, 22] found in ten out of 27 cases reviewed by one group. Finally, the presence of a tumor associated antigen in a carcinoma and the surrounding area affected with regional enteritis described by another group is of note.[10]

Summary and Conclusions

A case of carcinoma of the small intestine occurring in an affected area in a patient with Crohn's disease has been presented. In addition, 47 previously reported cases of the incidence of these two diseases in the same patient have been reviewed. Similarities and differences between small bowel carcinoma occurring spontaneously and that occurring in patients with Crohn's disease have been pointed out. The development of malignancy does appear to be a potential problem in patients with Crohn's disease. Perhaps criteria for operation in such patients should be re-evaluated.

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State of the Art*

The Management of the Patient with Short Bowel Syndrome

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Introduction

Management of the patient with short bowel syndrome (SBS) is an important problem and one which poses difficulties even for the most experienced gastroenterologist. In recent years, there have been considerable advances in our understanding of the pathophysiologic alterations that occur in short bowel syndrome and result in inordinate loss of fluids, electrolytes and nutrients. Application of this information has led to more rational therapy of patients with SBS.

It is the purpose of this review to focus on the management of the patient with short bowel syndrome with particular emphasis on newer therapeutic approaches. To illustrate the many types of problems encountered, a representative case is presented and fundamental principles of management are discussed in detail.

Case Report

A 47-year old male attorney first developed severe cramping abdominal pain in 1955 when he was 24 years of age. Because of unremitting abdominal pain, the patient underwent exploratory laparotomy and was found to have regional enteritis; an ileal resection was performed but it is not clear how much ileum was actually removed. From 1955-1973 the patient was essentially asymptomatic except for mild episodes of crampy abdominal pain and diarrhea. In 1973 he experienced a recurrence of abdominal pain, diarrhea and weight loss. He subsequently underwent intestinal resection and ileocolostomy. He experienced a stormy postoperative course, however, with intra-abdominal abscesses and fistulas. This necessitated two additional operations with resection of all but 120 cm. of small bowel distal to the ligament of Treitz and a jejunostomy. The rectum, sigmoid and left colon to the splenic flexure were left intact. There was residual disease, however, in this segment of colon.

Throughout the remainder of 1974 he was treated with a high carbohydrate, high calorie, high protein, fat-restricted diet with supplements of medium chain triglycerides. In addition, a trial of elemental diet formulations was also tried. In spite of these dietary manipulations, the patient lost 31.5 kg. in weight from 81-49.5 kg.

He was first admitted to the Kansas University Medical Center in February, 1975 because of severe malnutrition. He was severely cachectic and weighed only 46 kg. Pertinent findings at that time included the presence of severe anemia, hypokalemia, hyponatremia, hypocalcemia, hypoalbuminemia, hypocholesterolemia, azotemia and steatorrhea (Table I). Upper gastrointestinal x-rays revealed that the patient had very little small bowel beyond the ligament of Treitz (Fig. 1). He was initially treated with hyperalimentation and this effected a weight gain of approximately 6 kg. After this he was tried on a num-

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TABLE I

LABORATORY STUDIES

Study	Normal values	February, 1975	March, 1978
1. *Blood Studies*			
Hct.	(42-52%)	28%	44%
Hgb.	(12.5-16 gm./dl.)	9 gm.%	14 gm.%
Serum Na^+	(137-145 mEq./l.)	132 mEq./l.	141 mEq./l.
Serum K^+	(37-50 mEq./l.)	3.1 mEq./l.	4.1 mEq./l.
Serum Cl^-	(98-110 mEq./l.)	75 mEq./l.	100 mEq./l.
Serum CO_2	(23-28 mEq./l.)	40 mEq./l.	30 mEq./l.
BUN	(8-20 mg./dl.)	37 mg./dl.	12 mg./dl.
Serum creatinine	(0.5-1.2 mg./dl.)	3.0 mg./dl.	1.0 mg./dl.
Serum Ca^+	(9.0-11.0 mg./dl.)	7.5 mg./dl.	8.8 mg./dl.
Serum Mg^+	(1.4-2.3 mEq./l.)	0.6 mEq./l.	1.3 mEq./l.
Serum Albumin	(3.5-5.0 gm./dl.)	2.5 gm./dl.	4.2 gm./dl.
Serum Cholesterol	(150-250 mg./dl.)	90 mg./dl.	180 mg./dl.
Serum Folate	(7-16 ng./ml.)	2.4 ng./ml.	6.0 ng./ml.
2. *Fluid intake/24 hr.*		3,000-5,000 ml.	5,000-8,000 ml.
3. *Jejunostomy fluid/24 hr.*			
Volume		5,000-9,000 ml.	5,000-8,500 ml.
Na^+ output		200-500 mEq.	200-400 mEq.
K^+ output		60-150 mEq.	50-125 mEq.
Cl^- output		80-400 mEq.	80-400 mEq.
Ca^+ output		380-800 mg.	200-400 mg.
Fat output		40-70 gm.	25-45 gm.
4. *Weight*		46 kg.	72 kg.

ber of elemental diets. Due in part, however, to the hyperosmolarity of these preparations, he had inordinately high jejunostomy outputs with values as high as 9,000 ml./24 hr. Initially it was believed that the inordinate jejunostomy fluid losses could be corrected by increasing the patient's oral intake. It soon became evident, however, that merely increasing oral fluid intake up to 5,000 ml./day actually aggravated jejunostomy fluid losses with outputs up to 9,000 ml./day. Furthermore, provision of diets rich in simple sugars appeared to accentuate fluid and electrolyte losses.

Accordingly, in April, 1975 he was placed on a diet containing 3,500 calories. This was composed of 115 gm. of protein, 35-40 gm. of lipid, and 500-600 gm. of carbohydrate, the latter mostly in the form of starches. Other measures that were employed and the rationale for employing such measures are detailed in Table II. After institution of this regimen, the patient

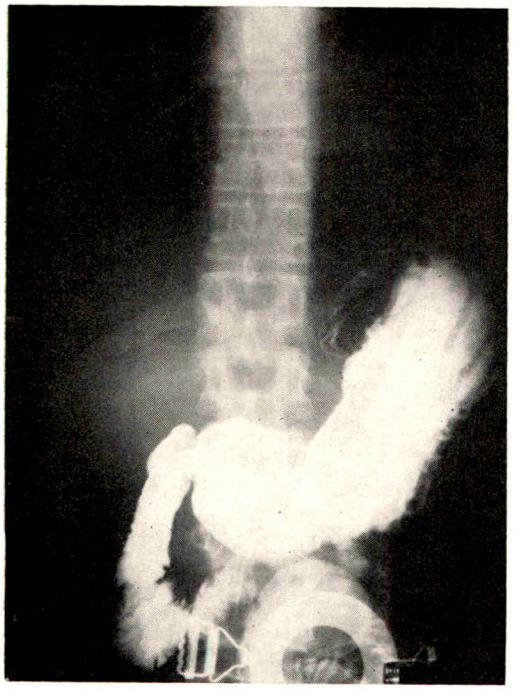


Fig. 1—Upper gastrointestinal roentgenogram showing very little remaining small bowel, which is somewhat dilated, and a jejunostomy. No residual inflammatory disease is apparent.

began to slowly gain weight at an average of .9 to 1.8 kg./mo. The patient himself made a number of interesting adaptions of his diet. First, he began ingesting very large quantities of starches, eating up to 24 rolls and muffins, additional slices of bread and several potatoes each day. Further, he began to cook his meat and poultry in a pressure cooker which he believed may have removed some of the lipid from the food. Other manipulations to increase his caloric intake included the use of large amounts of ketchup which provided additional calories. He also took much of his fluids in between meals as he had noted that eating fluids with his meals led to markedly increased flow of jejunostomy fluid shortly after the meal. A summary of the patient's diet and some of his interpretative comments are contained in Appendix A. It can be seen that he ingested 5,000-8,000 ml. of fluid and his jejunostomy outputs are 5,000-8,500 ml./day. He ate only three meals a day and these contained disproportionately large amounts of starch and very little simple sugar.

Over the course of the past two and one-half years, the patient has done remarkably well. He has gained approximately 26 kg. in weight and is currently asymptomatic. He is jogging three miles per day and is very active as a district judge.

Comment

This remarkable patient has taught me a great deal about appropriate management of SBS. That he has gained 26 kg. in weight is due in part to his ability to ingest inordinately large amounts of food and fluids. It is also related to increased absorptive capacity of the remaining small bowel. This notion is supported by the observation that in 1975 ingestion of 3,000-5,000 ml. of fluid and modest amounts of food resulted in jejunostomy outputs of 5,000-9,000 ml./24 hr. By contrast, in 1978 ingestion of larger amounts of fluid, i.e. 5,000-8,000 ml./day, along with enormous amounts of food have resulted in similar jejunostomy outputs of 5,000-8,500 ml./day. An additional factor contributing to the successful management of this patient is the patient's involvement in the program and his motivation and meticulous attention to detail.

Treatment of Short Bowel Syndrome

The major causes of short bowel syndrome are listed in Table III. The most common disorders resulting in short bowel syndrome are: 1. massive intestinal resection following a vascular insult to the small bowel and 2. regional enteritis with multiple bowel resections. Important principles in the management of patients with the short bowel syndrome are summarized in Table II. To begin with, the functional in-

TABLE II

MANAGEMENT OF SHORT BOWEL SYNDROME

Measure	Rationale
1. Assess functional integrity of remaining bowel	Will help determine dietary regimen
2. Medications to suppress inflammatory disease in remaining bowel	Residual inflammatory activity may further impair absorptive function
3. Dietary manipulations	
A. ↑ Calories to > 3,000/day	
B. High protein	
C. Carbohydrate, especially starches	↓ osmolarity (see text)
D. ↓ Fat intake to <40 gm./day	Fat → hydroxy fatty acids → cathartic effects (see text)
E. Elemental diets	↓ digestion required may enhance absorption
4. Vitamin and mineral supplements	
A. K^+ and Cl^- as KCl	$K^+ + Cl^-$ deficiencies and repair of metabolic alkalosis
B. Mg^{++} as $MgSO_4$	Mg^{++} deficiency
C. Ca^{++} and Vitamin D	Ca^{++} and Vitamin D deficiency
D. Trace metals (Zn, Ca, Mn, etc.)	Trace metal deficiency
E. Iron	Iron deficiency
F. Folate	Folate deficiency
G. Vitamin B_{12}	Impaired absorption with ileal disease and/or resection
H. Other vitamins (A,D,E,K,B_1,B_2,B_6,biotin)	Multiple vitamin deficiencies
I. Essential fatty acids	Avoid occult depletion of essential fatty acids
5. Measures to decrease motility and prolong mucosal contact time	
A. Belladona alkaloids	
B. Diphenoxylate (Lomotil®)	May also ↓ ileostomy outputs
C. Loperamide (Imodium®)	May also ↓ ileostomy outputs
D. Deodorized tincture of opium	
E. Codeine	Will ↓ ileostomy outputs
6. Special measures	
A. Use of by-passed colon to receive infusions of fluid and electrolytes	Residual colon can still absorb 1,000-1,500 ml. of fluid per day
B. Pancreatic extracts	Patients with malabsorption may have secondary pancreatic insufficiency; may have dilution of pancreatic enzymes
C. Cholestyramine	Bind bile salts and decrease their choleretic effects on net secretion of water and electrolytes by colon and small bowel
D. Cimetidine	Suppress massive gastric hypersecretion occasionally observed after extensive small bowel resection; decrease H^+ secretion and dilution of small bowel contents → ↑ concentration of pancreatic enzymes
E. Corticosteroids	May enhance water and electrolyte absorption by the colon and small bowel
F. Total parenteral nutrition	May be essential during first 2-6 weeks after massive intestinal resection
a. Temporary	
b. Long-term with silicone rubber catheter in superior vena cava[15]	

APPENDIX A

LOG OF PATIENT'S DIETARY INTAKE DURING A ONE-WEEK PERIOD

Effluent (ml.)	Urine (ml.)	Fluid intake (ml.)	Solids (oz.)
February 26, 1978: 5,975	950	5,865 (includes 775 milk)	6½ English muffins (4)* 5 creamed cheese (whipped) 18 pancakes (3) 4 creamed cheese 7 ground beef patties (2) 11½ potatoes (Betty Crocker sour cream and chives) 3 mozzarella cheese 2 buns (2) 3½ pan rolls (3) 2 pan rolls (2) 1 creamed cheese 2 Swedish rye bread 7¼ roast beef 8½ baked potato 3½ sour cream (cultured) 2¼ creamed cheese (whipped) 6 pan rolls (6) 1½ creamed cheese
February 27, 1978: 7,875	1,675	8,215 (includes 975 milk)	8 English muffins (4) 13¼ pancakes (2) 3¼ creamed cheese (whipped) 2¼ creamed cheese 16 goulash (ground beef, macaroni, tomatoes) 18 sweet potatoes 2¾ Swedish rye bread 2½ creamed cheese (whipped) 5 pan rolls (5) 4½ creamed cheese 5¼ smoked pork chops 2 Swedish rye bread 18¼ mashed potatoes 190 ml. gravy 1½ creamed cheese (whipped) 7½ pan rolls (5) 1½ creamed cheese
February 28, 1978: 8,650	1,500	7,915 (includes 850 milk)	6¾ English muffins (4) 18¾ pancakes (3) 3¼ creamed cheese (whipped) 3 creamed cheese 3½ roast beef 1½ mozzarella 4¾ onion buns 10 hash brown potatoes 7 pan rolls (6) 1¼ creamed cheese 1½ Swedish rye bread 15 rotini (with ground beef and meat sauce)

APPENDIX A (*continued*)

LOG OF PATIENT'S DIETARY INTAKE DURING A ONE-WEEK PERIOD

Effluent (ml.)	Urine (ml.)	Fluid intake (ml.)	Solids (oz.)
			14 scalloped potatoes (Betty Crocker) 2 home style bread 1¾ creamed cheese (whipped) 3 pan rolls (3) 1 creamed cheese
March 1, 1978: 7,950	1,200	6,650 (includes 1,100 milk)	7½ English muffins (4) 19 pancakes (3) 3 creamed cheese (whipped) 3½ creamed cheese
			9 buns (slightly moist) (3) 4½ roast beef 19 sweet potatoes 4½ pan rolls (3) 4½ creamed cheese
			18¾ mostaccioli (with ground beef and meat sauce) 4 home style bread 6½ baked potato 9¼ pan rolls (8) 2¼ creamed cheese (whipped) 3 creamed cheese
March 2, 1978: 7,500	1,325	7,165 (includes 1,150 milk)	6 English muffins (4) 21¼ pancakes (3) 3½ creamed cheese (whipped) 3½ creamed cheese
			13 rotini 7½ baked potato 3½ home style bread 3 sour cream (cultured) 1½ creamed cheese (whipped) 12½ pan rolls (12) 1½ creamed cheese
			2½ Velveeta 5 roast beef 4½ onion buns (2) 10 hash brown potatoes 7 pan rolls (6) 2 creamed cheese
March 3, 1978: 7,400	1,150	6,700 (includes 1,300 milk)	6 English muffins 21 pancakes (3) 2¾ creamed cheese (whipped) 4 creamed cheese
			3 mozzarella 1½ pastrami 3 roast beef 4¾ onion buns (2) 18 sweet potatoes 6½ pan rolls (6) 5¼ creamed cheese

APPENDIX A *(continued)*

LOG OF PATIENT'S DIETARY INTAKE DURING A ONE-WEEK PERIOD

Effluent (ml.)	Urine (ml.)	Fluid intake (ml.)	Solids (oz.)
			4 home style bread 14 potatoes (Betty Crocker sour cream and chives) 12 chicken (pressure cooked) 2½ creamed cheese (whipped) 6½ pan rolls (6) 1½ creamed cheese
March 4, 1978: 7,675	1,575	8,885 (includes 900 milk)	1½ bun 4½ English muffins (3) 17¾ pancakes (3) 3¾ creamed cheese (whipped) 3½ creamed cheese 12½ pizza (hamburger) 11 scalloped potatoes (Betty Crocker) 8 pan rolls (7) 2½ creamed cheese 9¼ roast beef 3 home style bread 11 baked potato 3 sour cream (cultured) 2 creamed cheese (whipped) 9 pan rolls (8) 3½ creamed cheese
March 5, 1978: 5,900	1,100	5,520 (includes 1,100 milk, of which 300 is estimated)	6¾ English muffins (4) 18 pancakes (4) 2 creamed cheese (whipped) 3½ creamed cheese 12½ veal parmigian 8½ baked potato 3½ home style bread 2½ creamed cheese (whipped) 7 pan rolls (6) 2 creamed cheese 3½ home style bread 4½ roast beef 14 mashed potatoes 150 ml. gravy (estimated) 2 creamed cheese (estimated) 9 pan rolls (8) 3¼ creamed cheese

* Number in parenthesis = number actually taken

Interpretative comments: All meats are the leanest I can buy and are trimmed of fat and with pork chops (which I can eat probably no more than once or twice a month) placed on a paper towel to absorb cooked-out fat. Once in a great while, I can find a really lean pork loin roast, which seems to cause no more difficulty than beef. I bake or broil everything, except that I "fry" pancakes and hash browns on a Teflon griddle without cooking oil. The prepared frozen meat casseroles (mostaccioli, rotini, lasagna, etc.) are relatively free of visible grease and the pasta contents are cooked to a very soft consistency, which makes them suitable for me. The entrées are frequently rechauffe, of course. The gou-

APPENDIX A *(continued)*

lash I buy is from the delicatessen department of a local store and very thoroughly cooked. Once in a while, I buy some of their other dishes. The milk is all ½%, which is the closest to skim I can buy. The sweet potatoes are vacuum packed, no syrup. (Only one brand of these is available locally.). The little gravy I eat is made from a package mix, not meat drippings, milk and flour. The only margarine I use is in mashed potatoes, about one and a half tablespoons. The reason for the inordinate number of pan rolls is that they take the place of dessert. They have a very faintly sweet taste, so faint it may not be detectable by one who eats sweets. I can eat them with creamed cheese in place of butter and wash them down with milk. I use whipped cream cheese in place of butter on other breadstuffs.

tegrity of the remaining small bowel should be assessed. In general, the absorption of nutrients will be influenced by: 1. extent and site of small bowel resected; 2. the presence of the ileocecal valve; 3. adaptation of the remaining small bowel and 4. the absorptive function of the remaining bowel as well as the function of related organs such as the gallbladder, pancreas and liver. In general, resection of up to 40-50% of the total length of the small bowel is usually well tolerated provided that the proximal duodenum, the distal half of the ileum and the ileocecal valve are spared. By contrast, resection of the ileum and the ileocecal valve alone may induce severe diarrhea and significant malabsorption even though considerably less than 30% of the small intestine is resected. There is evidence that adaptive changes occur in the small intestine following massive intestinal resection and that such adaptive changes may facilitate more efficient absorption by the remaining small intestine. This is usually reflected by an increase in caliber of the remaining segment of small intestine and can be demonstrated by barium contrast studies which often show dilatation of the bowel (Fig. 1). Such dilatation of the bowel may reflect an increase in the total absorptive surface of the remaining small intestine. It bears emphasizing that it may take six to 12 months for such adaptive changes to occur. Preliminary studies suggest that the hormones secretin and cholecystokinin-pancreozymin are important in adaptation, especially in patients receiving total parenteral nutrition.

There are few studies available, however, which have documented a compensatory increase in absorptive capacity in patients who have survived massive intestinal resection. To recapitulate, it is important to assess the functional integrity of the remaining small intestine as this will help determine the most appropriate dietary regimen. Such regimens are described below.

Suppression of residual inflammatory activity in remaining small bowel and colon:—In patients with short bowel syndrome due to regional enteritis and multiple intestinal resections, it is important to determine whether residual inflammatory disease activity is present. This may further impair intestinal absorptive function. In this regard, one could use the Crohn's disease activity index developed by the National Cooperative Crohn's Disease Study.[1] Alternatively, the following parameters could be checked: body weight, hematocrit, serum albumin level, erythrocyte sedimentation rate, presence of extraintestinal manifestations and presence of an abdominal mass. Importantly, if there is evidence of residual inflammatory activity, use of sulfasalazine and corticosteroids should be considered.

Dietary manipulations:—Dietary manipulations are important in the management of patients with short bowel syndrome. Oral feedings should be initiated as soon as possible. It is often necessary during a transition period, however, to continue parenteral hyperalimentation, albeit in reduced amounts. The diet should eventually con-

TABLE III

CAUSES OF SHORT BOWEL SYNDROME

1. *Compromised blood supply of the small intestine*
   - A. Thrombosis or embolism of superior mesenteric artery with subsequent massive intestinal resection
   - B. Thrombosis of superior mesenteric vein
   - C. Strangulated hernia
   - D. Volvulus of the small intestine
2. *Postsurgical*
   - A. Jejunoileal by-pass for morbid obesity
   - B. Inadvertent gastroileal anastomosis for peptic ulcer disease
   - C. Bowel resection after abdominal trauma
3. *Miscellaneous conditions*
   - A. Regional enteritis with multiple bowel resections
   - B. Primary neoplasms of the gut as well as intra-abdominal tumors involving the small bowel and colon
   - C. Radiation enteropathy

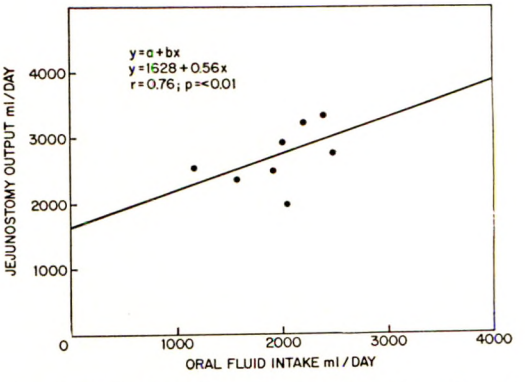


Fig. 2—Plot depicting the relationship of oral fluid intake to jejunostomy output in a 50-year old woman with short bowel syndrome and only 120 cm. of remaining small bowel following multiple resections for regional enteritis. The patient also has a jejunostomy. She is being maintained on deodorized tincture of opium (8 gtts. q.i.d. ac meals), tincture of belladonna (10 gtts. q.i.d. ac meals and h.s.), cimetidine (300 mg. q.i.d.) and a diet and mineral supplements similar to that described in the case study.

tain at least 3,000 calories/day. In our experience, diets high in protein, restricted in fat to less than 40 gm. of lipid per day and rich in carbohydrate have been particularly useful. In the past, it has been suggested that initial feedings should consist primarily of simple sugars which theoretically would require minimal digestion for effective absorption. There is preliminary evidence, however, indicating that simple sugars* which are not absorbed can pass into the colon where they are metabolized by colonic bacteria to lactic acid and other volatile fatty acids which can exert a cathartic effect.[2] Restricting simple sugars in the diet in patients with idiopathic ulcerative colitis has been shown to result in a marked decrease in the volume of stool and fecal excretion of volatile fatty acids and lactic acid.[2] Moreover, some preparations of simple sugars are somewhat hypertonic and may aggravate diarrhea because of an excessive osmolar load. Accordingly, we have administered carbohydrate in the form of starches and have observed a significant reduction in jejunostomy and ileostomy outputs. Jejunostomy output is also directly related to oral fluid intake (see case report and Fig. 2). Ordinarily, fluid intakes range from 2,500-3,500 ml. but in selected cases such as the patient described above, fluid intakes may be inordinately large.

Several studies have indicated that a fat-restricted diet (dietary lipid less than 40 gm./day) is effective in the symptomatic therapy of chronic diarrhea in patients with small bowel resection, especially after removal of the distal two thirds of the ileum.[3, 4] Such fat-restricted diets are likely to be more effective in patients who have not had a colectomy along with an extensive small bowel resection. For patients who have had a colectomy along with an extensive small bowel resection, a dietary regimen in which 50-75% of the long chain fat has been replaced by medium chain triglycerides has been beneficial in some

* Primarily monosaccharides and disaccharides.

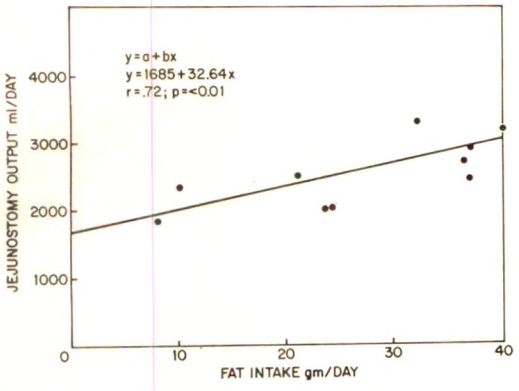


Fig. 3—Plot depicting the relationship between fat intake and jejunostomy output in the patient described in Figure 2.

patients and resulted in a further reduction in fecal water and electrolyte loss.[5] Data supporting the concept that reducing dietary fat intake to less than 40 gm./day is effective in reducing jejunostomy output in patients with SBS and colectomy is shown in Figure 3. It can be seen that there is a direct linear relation between dietary fat intake and jejunostomy output. The effectiveness of fat-restricted diets in reducing diarrhea is believed to be due to the fact that there is decreased production of hydroxy-fatty acids from long chain fats. Such hydroxy-fatty acids have been shown to have a cathartic effect and increase net secretion of water and electrolytes by the small bowel as well as the colon.[6-8]

In recent years there has been considerable interest in the use of elemental diets in the treatment of patients with short bowel syndrome. The rationale for using such elemental diets is that they require minimal digestion for effective absorption Many of the commercial preparations, however, are quite hypertonic. Accordingly, they must be diluted to avoid administering an excessive osmolar load which could in fact aggravate a patient's diarrhea. There have been few controlled studies which have actually demonstrated sustained weight gain and a marked reduction in jejunostomy output with the use of such elemental diets.

Vitamin and mineral supplements:—The rationale for providing vitamin and mineral supplements as well as the specific supplements required are summarized in Table II. Since jejunostomy and/or ileostomy outputs of potassium and chloride may be considerable (Table I), it is often necessary to provide up to 400 mEq. of chloride and 150 mEq. of potassium. Patients with short bowel syndrome are frequently magnesium-depleted. It is important to emphasize that such magnesium depletion can actually worsen diarrhea and that replacement with oral magnesium preparations is not only ineffective but may also further aggravate diarrhea. Accordingly, it is often necessary to give frequent injections of magnesium sulfate. An appropriate dose would be 2.0 ml. of a 50% solution of $MgSO_4$ given parenterally two to four times per week. Because calcium losses in jejunostomy fluid may also be considerable (Table I), it is often necessary to provide calcium supplements as well as Vitamin D. If the patient has developed frank hypocalcemia, 50,000 units of Vitamin D can be given orally daily for seven days and then twice weekly thereafter along with calcium supplements such as 0.5 gm. $CaCO_3$ q.i.d. With this regimen it is important to frequently check serum calcium and phosphorus levels. If the duodenum is diseased and/or bypassed, supplemental oral iron preparations will be poorly absorbed. In this setting, it is often necessary to give parenteral injections or intravenous infusion of iron preparations. Since Vitamin B_{12} is selectively absorbed in the ileum, it should be given to all patients with ileal resections greater than 80-100 cm. The usual dosage is 1,000 μg. every one to three months. In addition to the above-mentioned vitamins and minerals, trace metals such as zinc, cadmium

and manganese are frequently administered to avoid the development of a deficiency of such trace metals. Other vitamin needs and additional supplements are listed in Table II.

Measures to decrease motility and prolong mucosal contact time:—Belladonna alkaloids, diphenoxylate, imodium, deodorized tincture of opium and codeine have all been used as antidiarrheal agents but with variable results. In addition, self-administered intramuscular propantheline can be used to attain effective anticholinergic effects to control motility. Diphenoxylate and loperamide have been shown to reduce ileostomy outputs.[9] Codeine, in doses of 30-60 mg. p.o., is a very effective antidiarrheal agent but its long-term use is associated with a potential for addiction. If, however, all other measures fail, therapeutic doses of codeine may permit better control of diarrhea. While individual agents such as belladonna alkaloids and deodorized tincture of opium may have little beneficial effect when used alone, they may be more effective when used in combination. This is illustrated in the case presentation (Table II) and an additional patient whose clinical course is summarized in Figures 2 and 3.

Special measures:—Use of by-passed colon to receive infusions of fluid and electrolytes is an effective way of maintaining adequate plasma volume and normal renal function. Rogers and his associates have reported that this type of therapy can be of considerable benefit in the management of patients with short bowel syndrome.[10] In this regard, patients have received 1.5 l. of solution per rectum in a 24-hour period for periods as long as 14 months. Such therapy is based on the principle that the residual colon can still absorb 1,000-1,500 ml. of fluid per day.

Patients with short bowel syndrome may have secondary pancreatic insufficiency due to profound protein depletion. In addition, endogenously released pancreatic enzymes may be diluted by the inordinately large quantities of intraluminal fluid. For both of these reasons, patients with short bowel syndrome and persistent steatorrhea should receive a trial of pancreatic extracts. The use of cholestyramine in patients with short bowel syndrome is based on its ability to bind bile salt and decrease the choleretic effects of bile salts on small bowel and colonic mucosa thus reducing net secretion of water and electrolytes. Studies by Hofmann and Poley have shown that cholestyramine treatment of diarrhea associated with intestinal resection is most effective if the ileal resection is less than 100 cm. and fecal fat excretion less than 20 gm. of fat per day.[11] In the presence of extensive small bowel resection, it is necessary to markedly reduce the intake of dietary lipid in addition to using cholestyramine and substituting medium chain triglycerides for long chain triglycerides.[4]

Massive gastric hypersecretion has been documented in an occasional patient with extensive small bowel resection.[12] Fortunately, gastric hypersecretion in man after massive intestinal resection is usually a transient phenomenon and often acids outputs decrease to normal levels in patients who survive the acute effects of massive resection.[12] Rather than using antacids in such patients, there is preliminary evidence that cimetidine is effective in reducing gastric acid secretion.[13] Cimetidine treatment decreases both acid secretion and dilution of proximal small bowel contents; this results in a higher concentration of pancreatic enzymes. Furthermore, the increase in duodenal pH observed after cimetidine therapy can be expected to result in greater concentration of both bile salts and lipid in the micellar phase of intestinal contents.

This in turn should result in improved fat absorption. Finally, such treatment may result in decreased jejunostomy and ileostomy outputs.[13] Corticosteroids have been employed in patients with massive intestinal resection because there is preliminary evidence that they may enhance water and electrolyte absorption by the colon and small bowel.[5] Parenteral hyperalimentation may be essential during the first four to six months after massive intestinal resection. A detailed discussion of total parenteral nutrition is beyond the scope of this article, and the reader is referred to recent reviews of this subject.[14, 15] I would like to briefly cite, however, the studies of Jeejeebhoy, et al. In this investigation, total parenteral nutrition at home has been delivered to 12 patients surviving for periods ranging from four months to five years. The route used has been a silicone rubber catheter introduced into the superior vena cava. The delivery system is a simple pneumatic infusion set. The mean survival of uncomplicated catheters was about 16 months. All patients have maintained ideal body weight and have been socially rehabilitated with two exceptions. This study indicates that the total parenteral nutrition at home is feasible.

Miscellaneous Problems

Numerous studies have indicated that patients with ileal resection, massive small bowel resection and jejunoileal by-pass are prone to develop hyperoxaluria as a result of increased absorption of dietary oxalate.[16] The increased absorption of oxalate is related to several factors: 1. amount of dietary oxalate; 2. the intraluminal concentration of calcium; 3. the degree of steatorrhea; 4. the presence of a relatively intact colon and 5. the passage of increased amounts of bile salts into the colon. Perfusion of the isolated colon with oxalate and bile salts results in a markedly increased transmucosal passage of oxalate compared to perfusion with oxalate alone. The importance of the colon in enteric hyperoxaluria is underscored by the observation that patients with intestinal resection, steatorrhea and an intact colon have marked hyperoxaluria.[17] By contrast, patients with intestinal resection, a comparable degree of steatorrhea and a colonic resection do not have increased urine oxalate excretion.[17] These two lines of evidence indicate that the colon is the site of increased oxalate absorption in patients with small bowel resection.

Treatment of hyperoxaluria should include: 1. restriction of dietary oxalate; 2. reduction of dietary fat to less than 40 gm./day in patients with obvious steatorrhea and 3. cholestyramine, especially if the above measures are not effective. The mechanism of action of cholestyramine is believed to be the sequestration of bile salts thus preventing the bile salt-mediated enhancement of dietary oxalate absorption by the colonic mucosa.

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The Radiology Corner*

Collagenous Sprue

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Collagenous sprue is an uncommon cause of malabsorption. It is histologically characterized by the presence of mucosal atrophy and deposition of collagenous material in the subepithelial zone of the *lamina propria* of the jejunum.[2, 4] Typically, patients have progressive malabsorption which is often refractory to gluten restriction. In light of the poor prognosis frequently associated with collagenous sprue, the following case is presented to demonstrate the roentgenographic findings of this disease and the biopsy changes during the course of the disease.

Report of Case

E. V., a 57-year old man was admitted to the Waterbury Hospital Health Center with malaise and watery diarrhea.

The patient was in good health until 1965 when he developed diarrhea with two to three foul smelling bowel movements per day and a 15.5 kg. weight loss. His symptoms were intermittent over the next five years but his weight stabilized without medical treatment. Again, in 1970, the patient experienced diarrhea and weight loss. A small bowel biopsy was performed which was consistent with sprue. No collagen specific stains were performed but there did not appear to be any eosinophilic infiltrate in the *lamina propria*. He was placed on a gluten-free diet and did well.

One month prior to admission in 1975, the patient noted a recent 9 kg. weight loss and a flu-like illness with malaise, myalgias and diarrhea. At that time, he was not following a strict gluten-free diet. The diarrhea temporarily subsided but recurred. He began consuming large amounts of dairy products with further exacerbation of his diarrhea. On admission, the patient complained of abdominal cramping pain and four to five watery bowel movements per day. His presentation was further complicated by hematemesis, melena and epigastric burning.

Physical examination was unremarkable. Laboratory data included, hemoglobin, 13.0 gm./dl.; albumin, 2.1 gm./dl. (normal 3.0-5.5 gm./dl.); serum carotene, absent; Vitamin B_{12}, normal and serum iron, 24 mg./dl. (normal 50-150 mg./dl.). Prothrombin time was 70% of the control value, corrected to 100% following vitamin K administration. Stool was positive for occult blood but negative for infectious agents. Lactose tolerance test resulted in a flat blood glucose curve and abdominal cramping pain and diarrhea.

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Fig. 1—Small bowel series demonstrates moderate dilatation of the entire small bowel with prominence of the folds of the proximal portion.

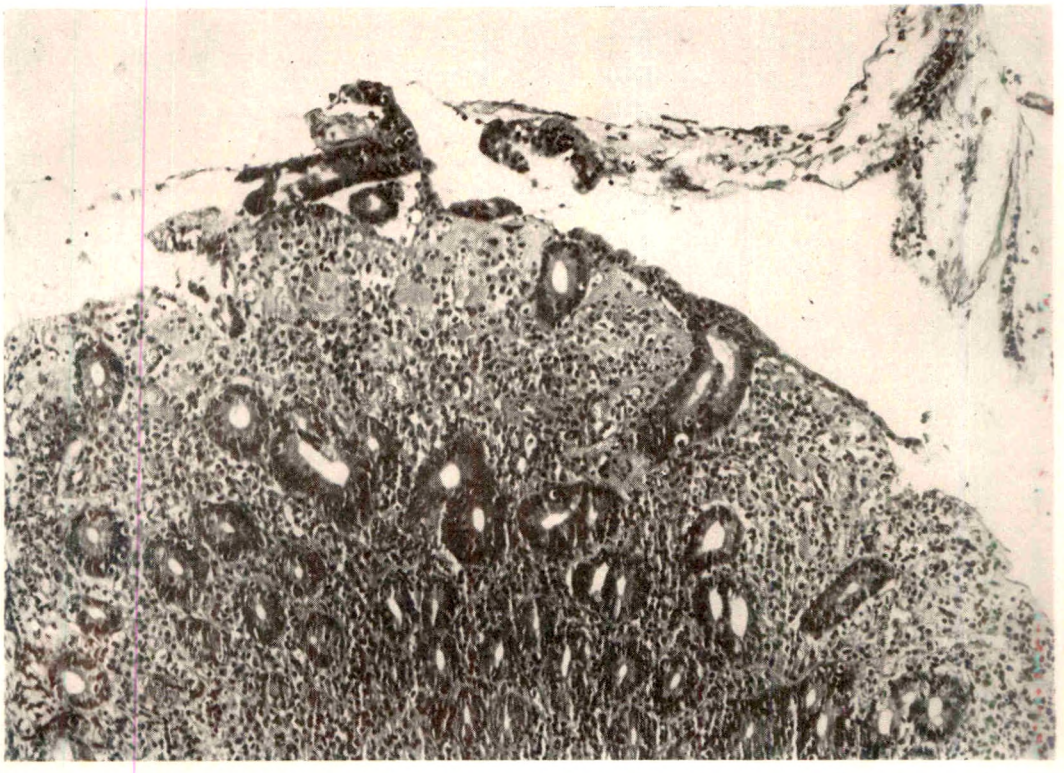


Fig. 2—Peroral biopsy of jejunum demonstrates marked villous atrophy with loss of normal architecture and collagenous deposition beneath the surface epithelium. An ulcerated pseudomembrane containing fibrin and neutrophils is present on the surface (Hematoxylin and eosin, original magnification x430).

Roentgenographic examination of the upper gastrointestinal tract revealed dilated small bowel distal to the ligament of Treitz and prominent mucosal folds in the proximal jejunum. (Fig. 1) Peroral biopsy of the jejunum demonstrated atrophy and loss of the villous architecture. In addition, excessive material staining for collagen was deposited beneath the surface epithelium in the *lamina propria*. Pseudomembrane formation with ulceration was also noted (Fig. 2).

Since this admission, the patient has followed a gluten and lactose-free diet with cessation of diarrhea and concomitant weight gain. Three months later, repeat biopsy at the ligament of Treitz revealed villous atrophy but a decrease in the amount of collagen deposition.

Comment

Previous reports[1-8] have emphasized that collagenous sprue is distinct from adult celiac disease. It has also been observed that 35% of patients with the latter entity have small foci of subepithelial collagen or eosinophilic depositis.[9] It is presently unclear if collagenous sprue is a separate disease or a severe variant of adult celiac disease. The patient under discussion demonstrated increasing symptoms associated with collagen deposition in the *lamina propria* of the small bowel and subsequent clinical improvement when col-

lagen decreased on biopsy. Although sampling artifact is possible, this suggests that collagen content may vary during the natural history of celiac disease and may be associated with more severe symptomatology.

All patients thus far reported with collagenous sprue have done poorly on a gluten-free diet at some point in their illness.[1-8] Severe hypoalbuminemia was a common feature and associated with a particularly poor prognosis.

Pepper, et al[5] reviewed nine cases of collagenous sprue. Four patients had small bowel dilatation and three others had thickened mucosal folds. These features do not allow distinction from simple adult celiac disease. In addition, our patient had a thickened small bowel wall and multiple mucosal ulcerations. These findings have been associated with vasculitis as seen in the connective tissues diseases and are not usually seen in simple adult celiac disease.[11]

In reviewing the previously reported cases of collagenous sprue[1-8] there were three patients with associated vasculitis.[3, 6] Five patients (including the three above) also had small bowel mucosal ulceration on biopsy.[1, 3, 6] Only two patients had bowel wall thickening.[6] In our case, these histologic features were also present and, combined with the roentgen appearance, suggest that an underlying connective tissue abnormality with vasculitis may be present.

The radiographic features of celiac sprue are well known and it is not possible on radiographic grounds alone to make a diagnosis of collagenous sprue. The radiologists, however, should be aware of this unusual entity and, in patients with small bowel radiographs with features of both vasculitis and celiac sprue, should suggest the diagnosis of collagenous sprue.

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The Last Page

QUESTIONS IN GASTROENTEROLOGY

MICHAEL RUOFF, M.D., F.A.C.G.*
New York, N. Y.

The Last Page appears as a regular feature in each issue of THE AMERICAN JOURNAL OF GASTROENTEROLOGY.

The questions that follow have been prepared exclusively from material in the current issue of the Journal and the page on which the answer can be found is indicated with each question.

One way for regular readers of the journal to utilize this feature is to scan *The Last Page* and attempt to answer the questions before reading the Journal. Then, when the articles have been read, return to *The Last Page,* again try to answer the questions and finally refer to the page locations that are provided in order to confirm your answers.

For each question, one or more responses may be correct, or none may be correct.

1. IN DOGS CIMETIDINE:

   A. Has no effect on serum gastrin except for a small increase in food-stimulated gastrin release when antral acidification is prevented.

   B. Potentiates an action of histamine which, at high doses inhibits pepsin secretion.

   C. Competitively inhibits histamine-stimulated acid secretion.

   D. Noncompetitively inhibits pentagastrin or urecholine stimulated acid secretion.

(Page 438)

2. THE USE OF LDH LEVELS TO DISTINGUISH BETWEEN MALIGNANT AND CIRRHOTIC ASCITES:

   A. Is simplified by the stability of LDH isoenzymes permitting freezing of the fluids and re-thawing and testing at a later date.

   B. Reveals that when the serum-to-ascites LDH ratio is less than unity, it is strongly suspicious of a malignant etiology of the ascites.

   C. Has shown that absolute levels of LDH can be relied upon to make the distinction.

   D. Is not reliable when the ascitic fluid is grossly bloody.

(Page 453)

3. THE PATTERN OF DISCORDANT SECRETION PRODUCED BY A STANDARD (SUBMAXIMAL STIMULATION) SECRETIN TEST IS:

   A. Characterized by extremely high flow and inappropriately low bicarbonate and normal enzyme secretion.

   B. Seen in hemochromatosis.

   C. Seen in cirrhosis.

   D. Only seen in alcoholics with manifest cirrhosis or manifest pancreatitis.

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4. MODIFICATIONS OF THE SECRETIN TEST CAN BE USED TO:

   A. Evaluate patency of the biliary tract.

   B. Obtain specimens for pancreatic cytology.

   C. Determine secretory capacity in patients with a marked secretory defect.

* Assistant Professor of Clinical Medicine, New York University School of Medicine.

D. Augment the qualitative and quantitative secretory defects in patients with chronic pancreatitis and pancreatic cancer, respectively.

(Page 459)

5. THE PATHOGENESIS OF PANCREATIC INFLAMMATION CAN BE ADEQUATELY EXPLAINED BY:

A. The presence of a common channel.

B. Biliary regurgitation.

C. The "big duct hypothesis".

D. The "small duct hypothesis".

(Pages 466 and 467)

6. THE RESPONSE OF THE PANCREAS TO ALCOHOLIC INJURY:

A. Is irreversible.

B. Is initially the accumulation of fat within parenchymal cells.

C. May include ductular reduplication.

D. May lead to ductular obstruction, stasis and protein plug formation.

(Page 470)

7. THE PHARMACOLOGIC ACTIONS OF SECRETIN INCLUDE:

A. Contraction of the gastroesophageal sphincter.

B. Relaxation of gastric muscular activity.

C. Increase in secretion of fluid and electrolyte by intestinal glands.

D. Increase in motor activity of the small and large intestines.

(Page 475)

8. SERUM AMYLASE ACTIVITY MAY BE RAISED IN THE ABSENCE OF CLINICAL PANCREATITIS IN:

A. Acute hypoxemia.

B. Renal insufficiency.

C. Codeine and morphine therapy.

D. Bronchogenic carcinoma.

(Page 481)

9. FUNCTIONAL SPLENECTOMY WITHOUT ACTUAL REMOVAL OF THE SPLEEN:

A. Can be obtained following blood clot embolization of the splenic artery.

B. May be complicated by splenic abscess formation.

C. Follows surgical ligation of the splenic artery.

D. Can be produced by intraarterial injection of tissue adhesives in dogs.

(Page 494)

10. POLYPS DEVELOPING IN THE POST-GASTRECTOMY STOMACH:

A. May be adenomatous, hyperplastic or examples of polypoid cystic gastritis.

B. Are "sentinels" of malignancy and can also undergo malignant transformation.

C. If present at the anastomosis are likely to be malignant.

D. Are a rare gastroenterologic curiosity.

(Page 496)

11. STUDIES OF SALICYLAZOSULFAPYRIDINE HAVE SHOWN THAT:

A. It is cleaved by colonic bacteria to 5-aminosalicylic acid and sulfapyridine.

B. The serum level of free sulfapyridine is significantly higher in patients in whom the drug has caused hemolysis.

C. Serum sulfapyridine levels are considerably higher in slow acetylators (60% of the West-European population).

D. On maintenance doses over 4.5 gm./day, over 50% of patients have some evidence of hemolysis.

(Page 504)

12. TOTAL PARENTERAL NUTRITION IN THE TREATMENT OF INFLAMMATORY BOWEL DISEASE:

A. Can lead to a long-lasting cure in many cases.

B. Helps to improve nutrition in the pre- and postoperative periods.

C. Aids in the management of gastrointestinal fistulas.

D. Is more helpful in ulcerative colitis than in Crohn's disease.

(Page 503)

13. EPIPHRENIC DIVERTICULA:

A. Are less likely to cause symptoms compared to traction diverticula of the mid esophagus.

B. Are generally small.

C. Are usually 0.5-1.0 cm. above the lower esophageal sphincter on the right side.

D. Are often associated with esophageal motility disorders.

(Page 510)

14. CHOLEDOCHAL CYSTS:

A. Commonly present in patients over 20 years of age.

B. Are often associated with the development of acute pancreatitis.

C. Are complicated by cholangitis, hepatic abscess, biliary cirrhosis, portal vein thrombosis and cyst rupture with peritonitis.

D. Are usually a diverticulum of the common bile duct.

(Page 518)

15. REVIEWS OF CARCINOMA OF THE SMALL INTESTINE IN REGIONAL ENTERITIS HAVE SHOWN THAT:

A. The incidence of small bowel carcinomas in patients with Crohn's disease is 0.08% a value higher than the 1 in 10^9 population which would be predicted if the two diseases were independent of one another.

B. The carcinomas in Crohn's disease occur in the proximal small intestine.

C. They may have a unique endometrial pattern of invasion.

D. Diagnosis and treatment tend to be delayed as the symptoms of the tumor are also symptoms of regional enteritis that are treated nonoperatively.

(Page 524)

16. THE SHORT BOWEL SNYDROME FOLLOWING MASSIVE SMALL BOWEL RESECTION IS MITIGATED BY:

A. Sparing of the distal ileum and ileocecal valve.

B. Functional integrity of remaining small intestine, pancreas, liver and gallbladder.

C. Adaptation of the remaining small bowel.

D. A diet rich in simple sugars rather than starches.

E. A liberal fat intake.

F. Cimetidine.

(Page 528)

17. COLLAGENOUS SPRUE:

A. Is often refractory to gluten restriction.

B. Has been shown to be a disease separate from adult celiac disease.

C. Should be suspected in patients with small bowel radiographs with features of both vasculitis and celiac sprue.

D. May cause small bowel mucosal ulceration identical to those commonly present in tropical sprue.

(Page 544)

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EDITORIAL

"State of the Art" Series

Medical "know-how" and technology has a tendency to advance by discontinuous leaps. Developments are certainly not time-dependent. It is not surprising, thus, that at any one time significant lapses in communication occur. Dr. Walter Harvey Jacobs has convinced the Editorial Board that these delays in dissemination of medical information can be remedied by appropriate "State of the Art" articles. He has undertaken to solicit those which are germain and with this issue initiates what I believe will be a section of the Journal extremely valuable to our readers.

The first of these is "The Management of the Patient with Short Bowel Syndrome" by Norton J. Greenberger, M.D., Peter T. Bohan Professor and Chairman, Department of Internal Medicine, The University of Kansas Medical Center College of Health Sciences and Hospital of Kansas City, KS. Among future articles will be "Therapeutic Strategies in Crohn's Disease" by Henry Janowitz, M.D. of New York, NY; "Intestinal Motility: Current Concepts" by Hooshang Meshkinpour, M.D., of Orange, CA; "The Training of a Gastrointestinal Endoscopist" by Angelo E. Dagradi, M.D., F.A.C.G. of Long Beach, CA and "Management of Patients with Polypoid Lesions of the Colon—Current Concepts and Controversies" by Joel F. Panish, M.D., F.A.C.G. of Beverly Hills, CA.

Many thanks Walter for what promises to be a job well done.

David A. Dreiling, M.D., F.A.C.G.

In Memoriam

We record with profound sorrow the passing of: A. Lawrence Abel, M.D., F.A.C.G., London, England, Honorary Fellow; Charles H. Best, M.D., F.A.C.G., Toronto, Canada, Honorary Fellow; Cuthbert E. Dukes, M.D., F.A.C.G., London, England, Honorary Fellow; William G. Fisher, M.D., F.A.C.G., New Orleans, La., Fellow; Rubin L. Gold, M.D., San Francisco, Calif., Member; Alfred Haas, M.D., F.A.C.G., New York, N. Y., Fellow; Lyle E. Heavner, M.D., Grosse Pointe, Mich., Member; Joseph S. Hepburn, M.D., F.A.C.G., Philadelphia, Pa., Life Fellow; Samuel L. Immerman, M.D., F.A.C.G., Philadelphia, Pa., Fellow; Jerome S. Levy, M.D., F.A.C.G., Little Rock, Ark., Life Fellow; Leo R. Miller, M.D., Boston Mass., Member; William Ostrow, M.D., F.A.C.G., New York, N. Y., Life Fellow; Sydney Rosenthal, M.D., F.A.C.G., Maplewood, N. J., Fellow; Herman Rubinstein, M.D., Long Island City, N. Y., Member; Henry G. Rudner, Sr., M.D., F.A.C.G., Memphis, Tenn., Fellow; William W. Weis, M.D., Piqua, Ohio, Member and James W. Wiltsie, M.D., F.A.C.G., Binghamton, N. Y., Life Fellow.

We extend our deepest sympathies to the bereaved families.

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NEWS NOTES

Course in Current Concepts, Controversies and Clinical Strategies in Gastroenterology

This course will be given 12-15 February 1979 and will consist of comprehensive coverage by 24 outstanding faculty for 300 participants, directed towards physicians and surgeons specializing, training, or with a particular interest in Gastroenterology. It will be presented by Cedars-Sinai Medical Center Departments of Gastroenterology and Medical Education at the Century Plaza Hotel, Los Angeles, California, Leslie J. Schoenfield M.D., Program Director. This course is approved for 26 hours of CME credit.

Further information may be obtained from Leslie J. Schoenfield M.D., Director, Department of Gastroenterology, Cedars-Sinai Medical Center, Box 48750, Los Angeles, CA, 90048.

A Symposium on Gastroenterology

The Division of Gastroenterology of the Department of Medicine and Extended Programs in Medical Education of the University of California School of Medicine, San Francisco, in cooperation with the Central California Committee on Gastroenterology, will present a Symposium on Gastroenterology. The program will address the diagnosis and management of acute and chronic diarrheas, malabsorption and the short bowel syndrome, peptic and gastric ulcer disease.

This program is approved for Category I credit of the Physician's Recognition Award of the American Medical Association and the Certification Program of the California Medical Association. For further information please contact: Extended Programs in Medical Education, University of California, Room 569-U, San Francisco, CA.

William Beaumont Gastrointestinal Symposium

The Eighth Annual William Beaumont Gastrointestinal Symposium for federal service physicians (Army, Navy, Air Force, Veterans Administration and Public Health Service) interested in the fields of gastroenterology or gastrointestinal surgery will be held at William Beamont Army Medical Center, El Paso, TX, 21-23 March 1979.

Further information may be obtained from John S. Gunther, M.D., LTC, MC, Chief, Gastroenterology Service, Post Office Box 70389, William Beaumont Army Medical Center, El Paso, TX 79920.

A Day in the G.I. Tract—An Update for the Generalist and Specialist

There will be a one day course, sponsored by the Division of Gastrointestinal and Liver Diseases of the Albert Einstein College of Medicine and Montefiore Hospital and Medical Center, for practicing internists, pediatricians, gastroenterologists, and family practitioners, who desire to keep abreast of developments in diseases of the gastrointestinal tract. It will emphasize pathophysiological, diagnostic and therapeutic aspects.

The course will be given on 29 April 1979 at the Riklis Auditorium, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY.

For further information contact: Office of Continuing Medical Education, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY 10461.

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BOOK REVIEWS FOR GASTROENTEROLOGISTS

Gastrointestinal Angiography, Saunders Monographs In Clinical Radiology—Vol. 1, 2nd ed.: by Stewart R. Reuter, M.D. and Helen C. Redman, M.D. 390 pages, illustrated. W. B. Saunders Company, Philadelphia, Pa., 1977. Price $27.50.

This is the first volume of the second edition of a series of monographs in clinical radiology. It is well done and adds considerable new information concerning the newer applications and technics of gastrointestinal angiography. The main value to me is the perspective gleaned from the past decade of experience in determining the clinical usefulness in various disease states.

DAVID A. DREILING, M.D., F.A.C.G.

Pathogenesis of Intestinal Infections: edited by M. V. Voino-Yasenetsky and T. Bakacs. 419 pages, illustrated. Akademiai Kiado Publishing House, Budapest, Hungary, 1977. Price $26.00.

This is a fine text representing a collaboration between Soviet and Hungarian physicians. It covers extensively an area, viz pathogenesis, pathology and microbiology which are generally limited to paragraphs in our clinically oriented parasitology texts. Particularly enjoyable and valuable is the inclusion of present research studies. Worth every penny.

DAVID A. DREILING, M.D., F.A.C.G.

Postgraduate Nephrology, 2nd edition: by Roger Gabriel, M.B. 238 pages, illustrated. Butterworths, Woburn, MA, 1978. Price $14.95.

Dr. Gabriel, a specialist in the treatment of renal diseases at St. Mary's Hospital in London, offered this monograph to help candidates prepare for the examination for admission as members in the Royal College of Physicians. It states on the fly leaf that this book also will appeal to senior Nephrological nurses and final year medical students. It seems that the book is written more for the latter group. As mentioned, the chapters are concise, probably a little too concise. Even though the book has been updated, the section on "Toxic Nephropathy, Due to Antibiotics," encompasses only about two-thirds of a page. Gentamicin is not mentioned in this section at all. This is a "nice little book," as mentioned above, for senior medical students and for nurses. It cannot be recommended for members in the medical profession at a more sophisticated level.

WALTER HARVEY JACOBS, M.D., F.A.C.G.

Atlas of Clinical Anatomy and Gross Anatomy Dissector: edited by Richard Snell, M.D. 430 pages, illustrated. Little, Brown, & Co., Boston, MA, 1978. Price for both $29.95.

Snell's *Atlas of Clinical Anatomy and Gross Anatomy Dissector* are extremely well done. They are more in the spirit of the Sobatta set than the Classical Anatomy of Gray. The color plates are beautiful. I particularly like the use of human subjects to illustrate anatomic points. Although intended for the medical student, the Atlas at least is of use to the surgeon and even perhaps the gastroenterologist who requires a quick reference of anatomy. Another group might profit, those facing anatomy review for licensure of boards.

DAVID A. DREILING, M.D., F.A.C.G.

Handbook of Clinical Pharmacology: edited by Felix Bochner, M.D., George Carruthers, M.D., Jens Kampmann, M.D. and Janice Steiner. 312 pages. Little, Brown & Co., Boston, MA, 1978. Price $9.95.

This is another one of those paperback handbooks which condenses and simplifies a generous segment of medicine. Excellent for an easy to use reference for drug usage.

DAVID A. DREILING, M.D., F.A.C.G.

Medicine: Essentials of Clinical Practice, 2nd edition: edited by Robert W. Wilkins, M.D. and Norman G. Levinsky, M.D. 1,050 pages. Little, Brown & Co., Boston, MA, 1978. Price, cloth edition, $25.00; paperback edition, $15.00.

This revised textbook of medicine is just what the medical school professor ordered. It is a simple, concise, easily readable reference which is invaluable for clinical clerks, interns and paramedics. The contributors, mainly faculty from the Boston University School of Medicine, have done a splendid job in percolating general medicine into a heady brew.

DAVID A. DREILING, M.D., F.A.C.G.

The Infection-prone Hospital Patient: edited by John F. Burke, M.D. and Gavin Y. Hildick-Smith, M.D. 250 pages. Little, Brown & Co., Boston, MA, 1978. Price $16.50.

It has been a long time coming but at last a monograph on hospital infection integrating clinical men, the surgeons, the house staff, and above

all, the administrators. A splendid multiauthored text, succinct informative and easy reading. Buy!

DAVID A. DREILING, M.D., F.A.C.G.

Interpretation of Diagnostic Tests: A Handbook Synopsis of Laboratory Medicine, 3rd Edition: Edited by Jacques Wallach, M.D. 639 pages. Little, Brown & Co., Boston, MA, 1978. Price $9.95.

I can see why this has gone into a 3rd edition and been translated into Spanish and Italian. It's good, up-to-date and useful. Excellent index. You can find what you are looking for.

The handbook is divided in 4 sections and 37 subsections with 79 tables. All laboratory tests are briefly described with clear expositions of abnormal findings and clinical usefulness.

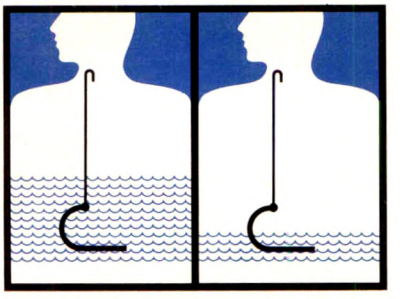
Wonderful for exam review and quick reference.

DAVID A. DREILING, M.D., F.A.C.G.

Progress in Gastroenterology, Vol. III: edited by George B. J. Glass, M.D. Grune & Stratton, Inc., New York, NY, 1978. Price $88.50.

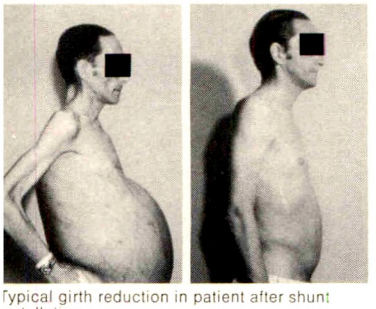
Jerzy Glass has done a fine job and maintained the standard of excellence in Volume 3 set by the two previous Progresses in Gastroenterology. He should not wait seven years for Volume 4. There are some 39 chapters grouped into seven areas such as Gastrointestinal Hormones, Endoscopy, Epithelial Kinetics, Oncology, Nutrition, etc. The contributors include a large number of foreign experts. Their inclusion, I believe, is a positive step in dissemination of gastroenterologic information.

DAVID A. DREILING, M.D., F.A.C.G.

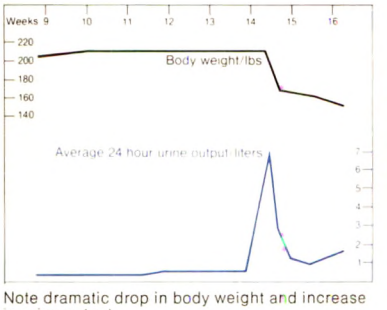


The LEVEEN Peritoneo-Venous Shunt.

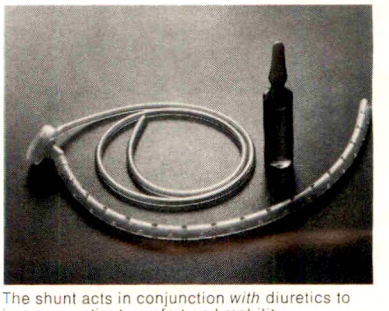
A device that can contribute significantly to the medical treatment of refractory ascites.



Typical girth reduction in patient after shunt installation.



Note dramatic drop in body weight and increase in urine output.



The shunt acts in conjunction *with* diuretics to increase patient comfort and mobility.

Refractory ascites has traditionally been a medically-managed problem, often complicated by increased aldosterone, creatinine and BUN levels, reduced sodium clearance, and progressively increasing oliguria. The treatment of choice, which usually includes a salt-restricted diet and a regimen of powerful diuretics, eventually may only mobilize the ascitic fluid at the expense of renal function. The patient often requires repeated hospitalization as fluid becomes more and more difficult to mobilize, and increased girth, breathing difficulty, nutritional deficiency and renal complications reduce the patient's mobility, comfort and longevity.

Not a cure or a solution by itself, but, combined with diuretic treatment, a promising improvement in patient comfort and longevity[2].

Easily implanted, the LEVEEN Peritoneo-Venous Shunt offers another tool to simplify this usually difficult course of patient management. By means of a pressure-activated valve with attached tubing, the shunt routes fluid from the peritonel cavity into the superior vena cava. Thus by increasing the intravascular fluid, the shunt may help to prevent or actually reverse the hepato-renal syndrome[5], while it can allow a wider safety margin for the use of diuretics without causing kidney damage.

Urine output increased, girth reduced.

Studies have shown that patients with the shunt implanted usually present a drop in aldosterone, creatinine, and BUN levels, with increased sodium clearance, urine output, and reduced girth and body weight. All of these results usually occur within 24 hours after shunt installation.[1-6] In one 1977 study of 28 patients, mean urine flow increased from 607 ml to 4,254 ml, mean abdominal girth dropped from 108 to 93 cm, mean BUN level fell from 39 to 23 mg/100 ml, and the mean plasma creatinine level was reduced from 2.4 to 1.8 mg/100 ml[4].

More mobility, less hospitalization.

In the same 1977 study, most patients were discharged within 10 to 15 days after surgery, and after 18 months, nearly half were still alive. Of patients who had a bilirubin value of less than 10 mg/100 ml and no signs of severe encephalopathy or recent GI bleeding, 71% were alive after 18 months.[4] Even after shunt implantation, patients still require medical attention, but will not, in most cases, remain hospital-bound, and will require less of the physician's time. Increased patient comfort and reduced hospital dependency will restore some degree of mobility and normality to the ascitic patient.

Call for technical information.

An increasing number of physicians are discovering this simple device can indeed augment medical treatment of a difficult problem. **For your copy of the studies and relevant product data, write to:**

Mr. Ralph Colling
Becton, Dickinson and Company
Rutherford, N.J. 07070
or call this toll free number for answers to your technical questions: 800-631-0174.

BECTON-DICKINSON Division of Becton, Dickinson and Company, Rutherford, N.J. 07070

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Indications For Use:
The LeVeen Peritoneo-Venous Shunt may be indicated when the patient does not respond promptly to intensive medical management.

The shunt is designed to eliminate the accumulation of ascitic fluid. Shunt placement should be considered for treatment of ascites complicating the following conditions:

1. Cirrhosis
2. Budd-Chiari Syndrome
3. Chylous Ascites
4. Nephrogenic Ascites
5. Biliary Atresia
6. Amyloidosis
7. Cryptogenic Ascites

Contraindications For Use:
In certain patients, the LeVeen Peritoneo-Venous Shunt will not be effective, or may be contraindicated because of secondary complications that outweigh its benefits. These conditions are:

1. **Peritonitis.** This should always be suspected when the peritoneal fluid is turbid. Peritonitis can occur without the usual signs and symptoms in patients with ascites.
2. **Esophageal Varices.** With A Recent History Of Bleeding. If ascites and variceal bleeding are present concurrently, treating the varices first may be indicated.
3. **Renal Failure.** The shunt will not reverse the renal damage in patients with acute tubular necrosis or other types of primary renal failure. A low urine sodium concentration may be the best indication that the tubules are functional and may respond to a shunt.
4. **Bilirubin level above 10 mg/dl**

Cautions:

1. **Esophageal Varices.** Without Recent Bleeding. In patients whose varices have been treated surgically, the shunt may be effective.
2. **Neoplastic Ascites.** The LeVeen Peritoneo-Venous Shunt has been used with success in patients with intractable ascites associated with primary or metastatic intra-abdominal neoplasms.[3] The use of the shunt in such patients requires weighing the shunt's potential benefits against the possible hazard of generalized dissemination of neoplastic cells which are commonly present in the ascitic fluid of these patients.
3. **Associated Cardiac Disease.** Cardiac patients may be sensitive to increased blood volume due to sudden recirculation of large quantities of ascitic fluid. Removal of accumulated ascitic fluid from the abdomen at the time of shunt placement may be indicated in such patients.

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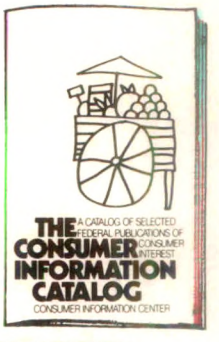
"I CAN HELP CHANGE YOUR LIFE. BUT I CAN'T HELP CHANGE YOUR SPARK PLUGS."



If you want to find inner peace, come see me. But ask me how to fix a car? You got me. For questions of that nature, you must seek knowledge somewhere else.

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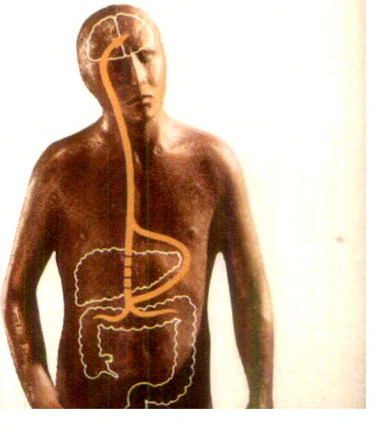
DOSAGE AND ADMINISTRATION: The usual dosage is 2 to 3 tablespoonfuls (30 to 45 ml., containing 20 g. to 30 g. of lactulose) three or four times daily. The dosage may be adjusted every day or two to produce 2 or 3 soft stools daily. Hourly doses of 30 to 45 ml. of Cephulac may be used to induce the rapid laxation indicated in the initial phase of the therapy of portal-systemic encephalopathy. When the laxative effect has been achieved, the dose of Cephulac may then be reduced to the recommended daily dose. Improvement in the patient's condition may occur within 24 hours but may not begin before 48 hours or even later. Continuous long-term therapy is indicated to lessen the severity and prevent the recurrence of portal-systemic encephalopathy. The dose of Cephulac for this purpose is the same as the recommended daily dose.

Product Information as of August, 1975

References:

1. Schomerus, H. and Hamster, W.: Latent portasystemic encephalopathy. Digestion 14:548-549, 1976.
2. Smith, H.H. and Smith, L.S.: WAIS functioning of cirrhotic and non-cirrhotic alcoholics. J. Clin. Psychol. 33:309-313, 1977.
3. Rikkers, L., Jenko, P., Rudman, D. and Freides, D.: Subclinical hepatic encephalopathy: detection, prevalence, and relationship to nitrogen metabolism. Gastroenterology 72:1119, 1977.

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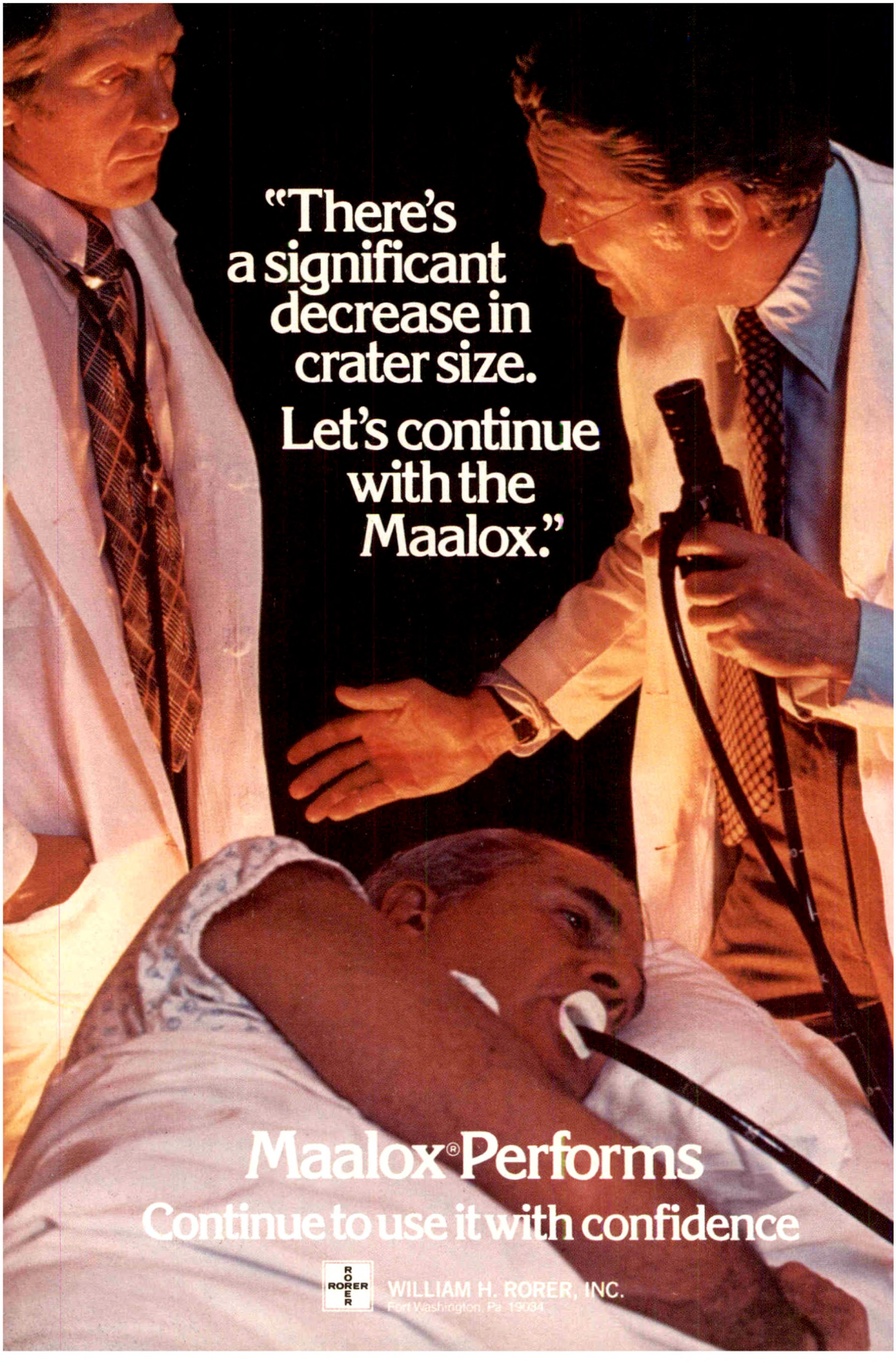
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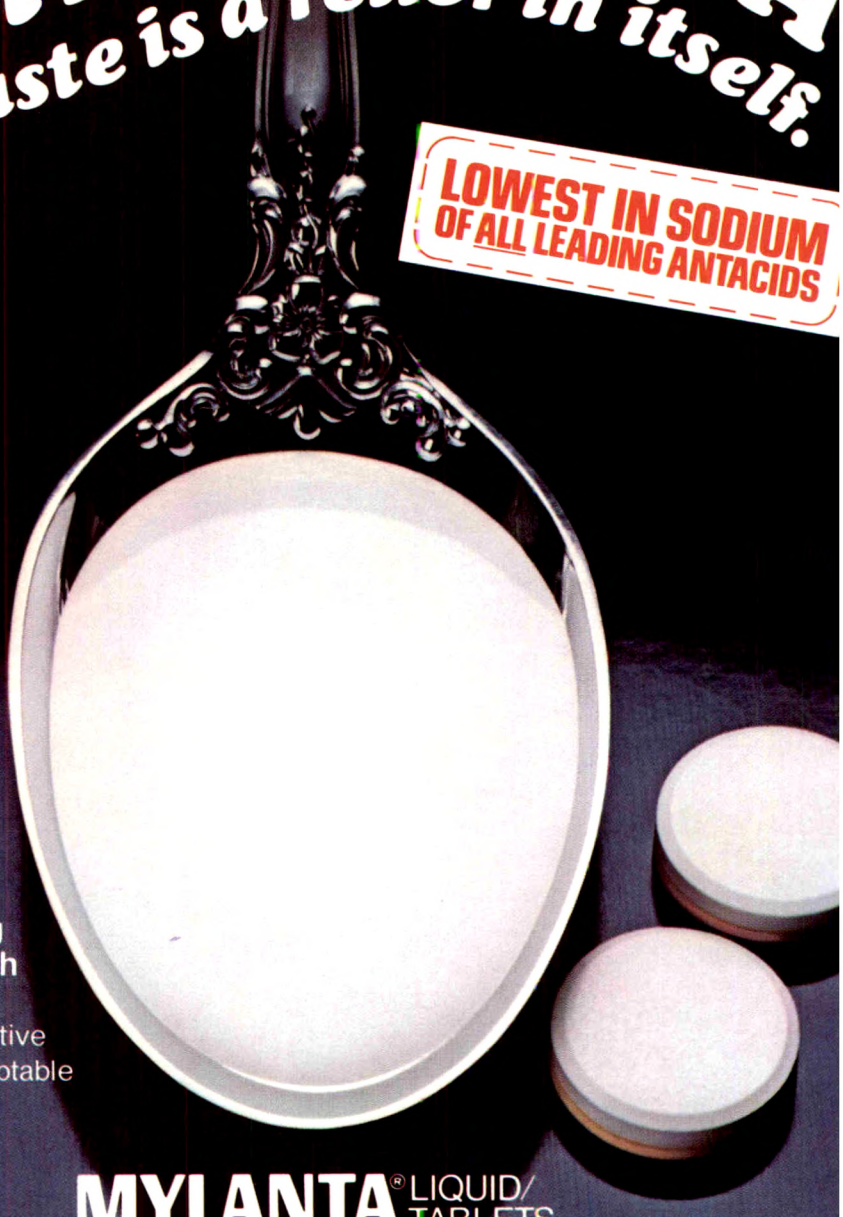
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Each table should be typed double-spaced, including all headings and each should begin on a separate sheet of 8½ × 11 inch paper. Larger size sheets should not be used. If a table must be continued, a second sheet of 8½ × 11 inch paper should be used and the heads of all columns and lines should be repeated. All tables should be arranged so that when they are printed they will not be wider than the width of the type of one page (5½").

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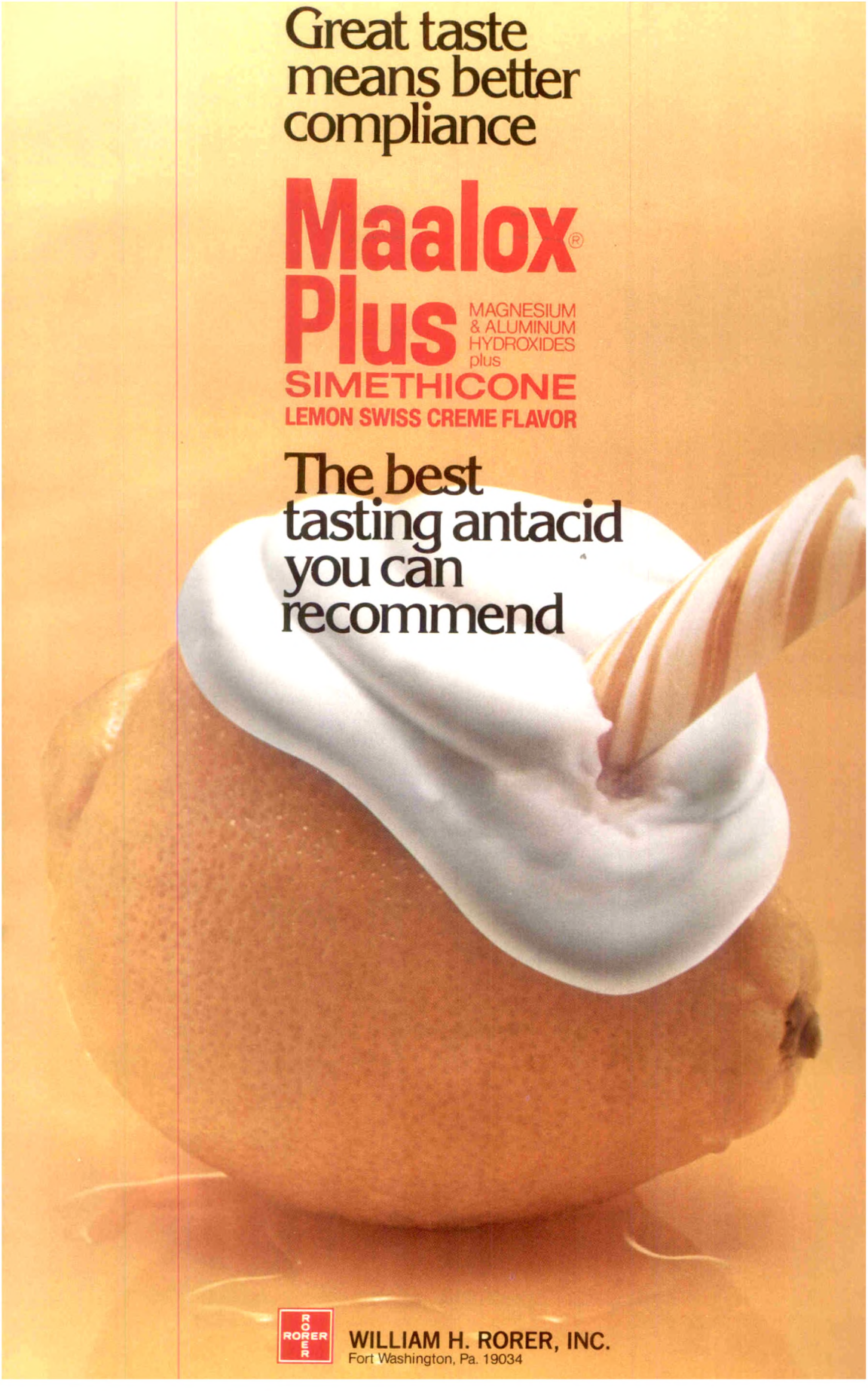
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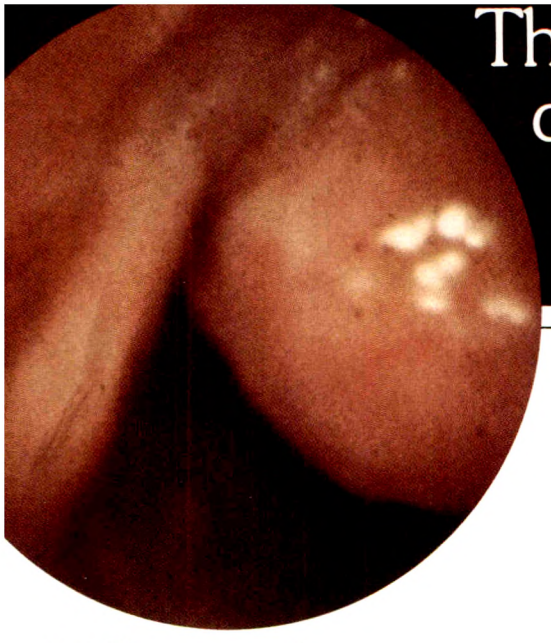
LEMON SWISS CREME FLAVOR

The best tasting antacid you can recommend



RORER

WILLIAM H. RORER, INC.
Fort Washington, Pa. 19034



The patient has dysphagia of 1½ years' duration.

Physical exam is unrevealing.
X-ray studies are inconclusive.

What is the diagnosis?

Esophagoscopy resolves the question.

A 56-year-old man was seen because of increasingly severe dysphagia of one and a half years' duration. At the time of admission, the patient could take only liquids. Physical examination was unrevealing.

A filling defect of the midesophagus was observed by the radiologist. On several projections it appeared to be extrinsic, although an intrinsic lesion, such as leiomyoma, could not be excluded.

Esophagoscopy was performed, and a round submucosal tumor thought to be a *leiomyoma* was identified at the level of 28 cm from the incisor teeth. The patient refused surgical intervention.

Causes of dysphagia may include esophageal carcinoma, achalasia, lower esophageal ring or esophageal web, as well as benign neoplasm. Benign tumors are rare and when detected are usually only incidental findings. Such tumors may, however, become symptomatic upon reaching a large enough size. Such tumors are most often *leiomyomas*, which can partially obstruct the esophageal lumen. Characteristically, they develop central ulceration and hemorrhage.

Case discussion based on *The Clinical Significance of Esophagoscopy* by Bernard M. Schuman, M.D., one in a series of monographs made available by Roche Laboratories in fulfillment of its commitment to continuing education in gastroenterology. This case history illustrates the diagnostic use of endoscopy; it does not represent an indication for Librax therapy.

Endoscopy

–confirmatory or contradictory–

a valuable aid in the diagnosis of G.I. disorders

The development of highly specialized fiberoptic endoscopes has significantly enhanced the accuracy and efficiency of gastrointestinal diagnosis and treatment. Frequently, when both x-ray and laboratory tests have been repeatedly negative, endoscopy has uncovered an organic lesion.

Whether a G.I. condition is eventually confirmed as functional or organic, every patient should receive a thorough examination of his emotional profile and life stresses; such factors may give rise to the patient's symptomatic complaints or aggravate the symptoms of an organic disorder.

Librax®: a valuable aid in the treatment of irritable bowel syndrome*

The diagnosis of irritable bowel syndrome is based on the patient's symptoms and history, plus the exclusion of an organic disorder. In this condition, Librax has been found doubly valuable as an adjunct to reassurance and counseling because it relieves distressing symptoms of both emotional and somatic origin.

1 Only Librax provides the specific antianxiety action of Librium® (chlordiazepoxide HCl), in addition to the antisecretory-antispasmodic actions of Quarzan® (clidinium Br)—both original developments of Roche research.

2 Librax seldom impairs mental acuity or performance when given in proper dosage. However, as with all preparations containing CNS-acting agents, patients should be cautioned against hazardous occupations requiring complete mental alertness.

3 Flexibility of dosage helps meet varying requirements: 1 or 2 capsules three or four times daily, before meals and at bedtime.

4 The convenience and economy of a single Rx help sustain patient compliance, while providing relief of both emotional and somatic symptoms.

A distinctive antianxiety-antispasmodic agent

Librax®

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium Br.

ROCHE

*Librax has been evaluated as possibly effective for this indication.
Please see brief summary of prescribing information on following page.

Librax®

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium Br.

Please consult complete prescribing information, a summary of which follows:

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows: "Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Physical and psychological dependence rarely reported on recommended doses, but use caution in administering Librium® (chlordiazepoxide HCl) to known addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions) reported following discontinuation of the drug.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.**

As with all anticholinergics, inhibition of lactation may occur.

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established.

Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.

Dosage: Individualize for maximum benefit. Usual maintenance dose is 1-2 capsules, 3-4 times/day, before meals and at bedtime. Geriatric patients—see Precautions.

How Supplied: Available in green capsules, each containing 5 mg chlordiazepoxide HCl (Librium®) and 2.5 mg clidinium Br (Quarzan®)—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 50, singly and in trays of 10.

ROCHE

Roche Products Inc.
Manati, Puerto Rico 00701

MEETINGS OF INTEREST

44th Annual Convention, American College of Gastroenterology, Disneyland Hotel, Anaheim, CA, 22-24 October 1979.

Annual Course in Postgraduate Gastroenterology, American College of Gastroenterology, Disneyland Hotel, Anaheim, CA, 25-27 October 1979.

A Symposium on Gastroenterology, University of California School of Medicine, San Francisco and the Central California Committee for Gastroenterology, Ahwahnee, Yosemite National Park, CA, 11-14 March 1979.

Eighth Annual William Beaumont Gastrointestinal Symposium, William Beaumont Army Medical Center, El Paso, TX, 21-23 March 1979.

Inflammatory Bowel Disease: Experience and Controversy, Teaching Seminar co-sponsored by the American College of Gastroenterology and Lenox Hill Hospital, Einhorn Auditorium, Lenox Hill Hospital, New York, NY, 20, 21 April 1979.

A Day in the G.I. Tract—An Update for the Generalist and Specialist, Divisions of Gastrointestinal and Liver Diseases, Albert Einstein College of Medicine and Montefiore Hospital and Medical Center, Riklis Auditorium, Albert Einstein College of Medicine, Bronx, NY, 29 April 1979.

Current Concepts in Gastrointestinal Disease, Postgraduate Course of the American Gastroenterological Association, Rivergate Convention Center, New Orleans, LA, 19, 20 May 1979.

Eightieth Annual Meeting of the American Gastroenterological Association, New Orleans Hilton, New Orleans, LA, 21-23 May 1979.

Endoscopy 1979, Postgraduate Course of the American Society for Gastrointestinal Endoscopy, New Orleans, LA, 24, 25 May 1979.

Which type of duodenal ulcer patient benefits most from 'Tagamet'?

- ☐ newly diagnosed patients
- ☐ duodenal ulcer repeaters
- ☐ refractory patients
- ☐ hospitalized patients
- ☑ all of the above

Tagamet®

brand of cimetidine

Tablets, 300 mg. Injection, 300 mg./2 ml.



SK&F LAB CO.
a SmithKline company

Please see last page of this ad for brief summary of prescribing information.

Tagamet®–For All Types

Tablets, 300 mg. Injection, 300 mg./2 ml.

brand of **cimetidine**

Provides effective symptom relief, day and night

"Patients taking cimetidine showed a rapid increase in the number of pain-free days, and this number was significantly different from that in the placebo group in all treatment weeks....A similar trend was seen with respect to pain-free nights.[1]"

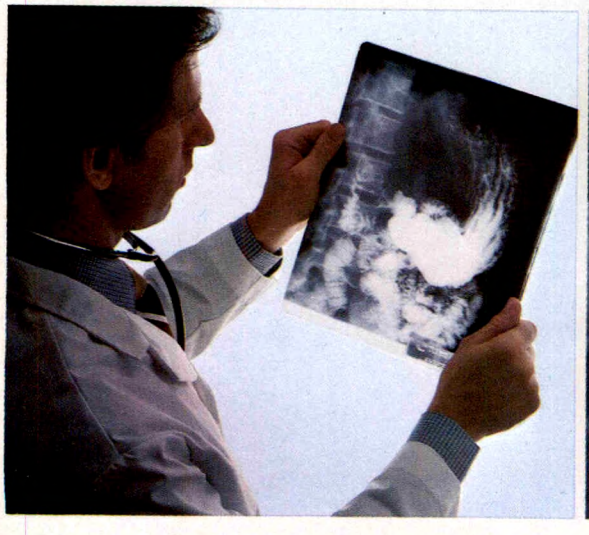
(From a double-blind study in 33 patients who received 'Tagamet' 300 mg. q.i.d. and 34 who received placebo, for six weeks.)

"Symptomatic improvement in patients given cimetidine was usually marked and occurred early...significant clinical improvement occurred in cimetidine-treated patients compared with placebo, as judged by the patients themselves and by the numbers of patients who became symptom-free during treatment.[2]"

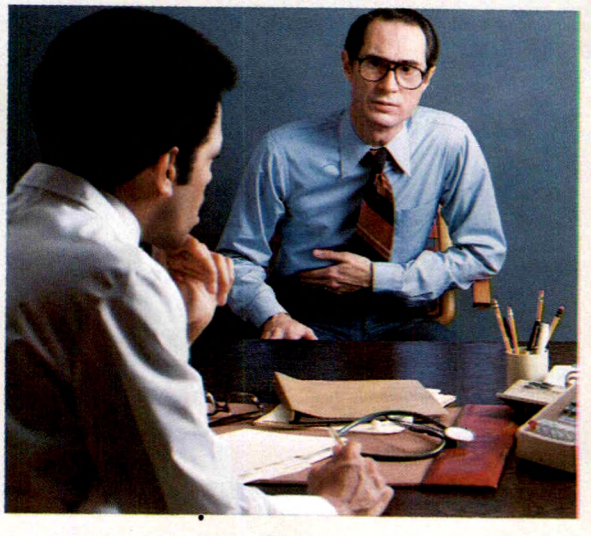
(From a double-blind study in 65 duodenal ulcer patients who received 'Tagamet' 1 or 1.2 Gm./day and 24 who received placebo, for four weeks.)

1. Hetzel, D.J., et al.: Cimetidine in the treatment of duodenal ulcer. M.J. Australia 1:317-319 (Mar. 5) 1977.
2. Bardhan, K.D., et al.: The effect of cimetidine on duodenal ulceration: An interim report of a multicenter double-blind trial. Proceedings of the Second International Symposium on Histamine H_2-Receptor Antagonists. Excerpta Medica, pp. 260-271, 1977.
3. Gray, G.R., et al.: Oral cimetidine in severe duodenal ulceration. Lancet 1 (8001):4-7 (Jan. 1) 1977.

newly diagnosed patients



duodenal ulcer repeaters



of Duodenal Ulcer Patients

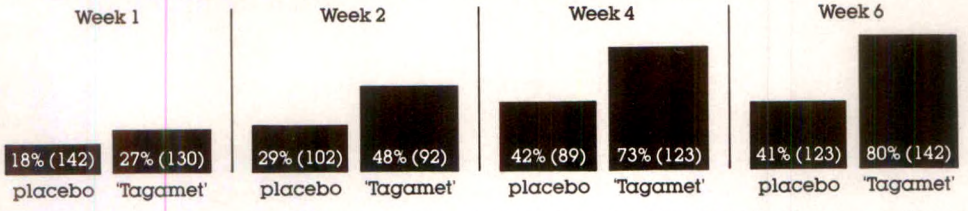
And promotes rapid ulcer healing

> "After twenty-eight days, 17 of 20 (85%) patients receiving cimetidine showed ulcer healing, compared with 5 of 20 patients receiving placebo ($P < 0.0005$).[3]"

> "Forty-seven (72%) of 65 patients treated with cimetidine had healed ulcers compared with 7 (29%) receiving placebo.[2]"

> "This study demonstrates that ulcers of patients treated with cimetidine (1.2 g./day) have a significantly higher healing rate (82%) than those of patients receiving placebo (39%).[1]"

Incidence of Duodenal Ulcer Healing* Relative to Duration of Treatment [4]
(Numbers in parentheses are numbers of patients analyzed)



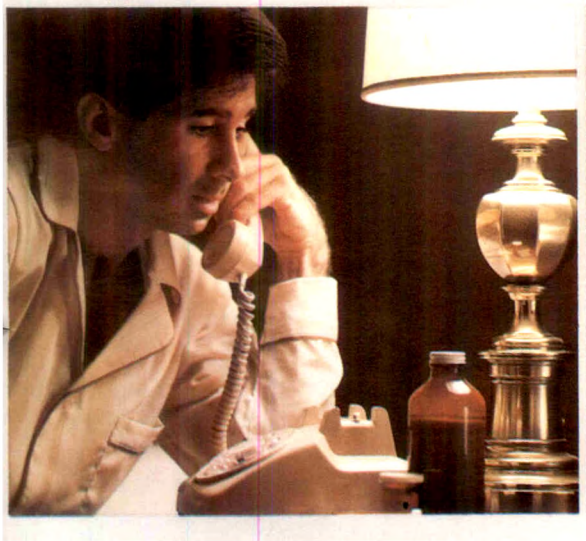
Daily dosage ranged from 0.8 to 2.0 Gm.; five of the studies used 1.2 Gm./day. All patients were permitted p.r.n. antacids for relief of pain.

*In all studies, both presence of ulcer and ulcer healing were endoscopically confirmed.

4. Data from eight double-blind studies summarized by Winship, D.H.: Cimetidine in the treatment of duodenal ulcer. Review and commentary. Gastroenterology 74:402-406 (Feb.) 1978.

Please see following page for a brief summary of prescribing information.

refractory patients



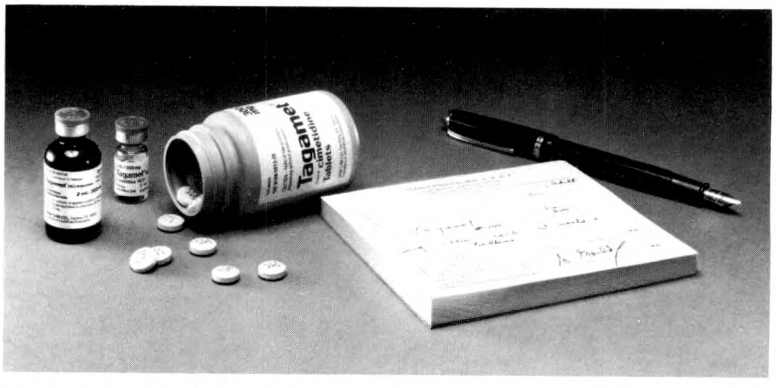
hospitalized patients



Tagamet® brand of cimetidine

Tablets, 300 mg. Injection, 300 mg./2 ml.

For all of your duodenal ulcer patients
- Effective symptom relief, day and night
- Rapid ulcer healing
- Well tolerated



Dosage in Duodenal Ulcer
The recommended dosage is 300 mg. four times a day, with meals and at bedtime. Treatment periods should not exceed eight weeks.

While healing may occur during the first week or two, 'Tagamet' therapy should be continued for four to six weeks unless healing has been confirmed.

Concomitant antacids should be given as needed for relief of pain.

Dosage should be reduced in patients with impaired renal function.

Before prescribing, see complete prescribing information in SK&F literature or PDR. The following is a brief summary.

Indications: 'Tagamet' (brand of cimetidine) is indicated in the short-term (up to 8 weeks) treatment of duodenal ulcer; and in the treatment of pathological hypersecretory disorders (i.e., Zollinger-Ellison syndrome, systemic mastocytosis and multiple endocrine adenomas). Concomitant antacids should be given as needed for relief of pain. Studies to date do not provide evidence of the safety of cimetidine in uncomplicated duodenal ulcer beyond 8 weeks.

Contraindications: There are no known contraindications to the use of 'Tagamet'.

Precautions: In a 24-month toxicity study in rats at dose levels approximating 9 to 56 times the recommended human dose, benign Leydig cell tumors were seen. These were common in both the treated and control groups, and the incidence became significantly higher only in the aged rats receiving 'Tagamet'. Reproduction studies in animals have shown no evidence of impaired mating performance or fertility.

Lack of experience to date precludes recommending 'Tagamet' for use in pregnant patients, women of childbearing potential, nursing mothers or children under 16 unless anticipated benefits outweigh potential risks; generally, nursing should be discontinued in patients taking the drug. Symptomatic response to 'Tagamet' therapy does not preclude the presence of a gastric malignancy.

Adverse Reactions: Diarrhea, muscular pain, dizziness, rash, mild gynecomastia. A few cases of reversible confusional states have been reported, usually in elderly and/or severely ill patients. A few cases of neutropenia have been reported, but no causal relationship could be established. Increased serum transaminase and creatinine, as well as rare cases of reversible fever and interstitial nephritis, have been reported; these cleared on withdrawal of the drug.

How Supplied: Pale Green Tablets: 300 mg. tablets in bottles of 100 and Single Unit Packages of 100 (intended for institutional use only).

Injection: 300 mg./2 ml. in single-dose vials and in 8 ml. multiple-dose vials in packages of 10.

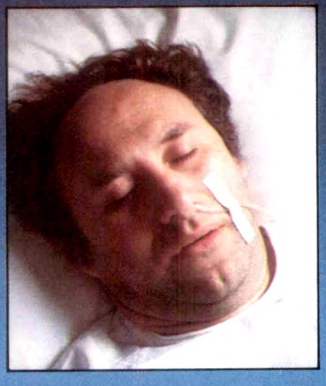
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a SmithKline company

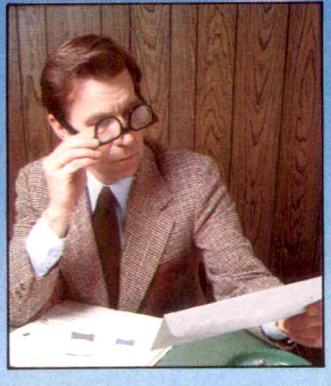
Date of issuance Oct. 1978

SK&F LAB CO., Carolina, P.R. 00630

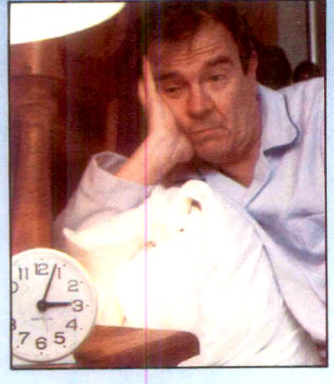
Which of these cirrhotic patients has portal-systemic encephalopathy (PSE)?

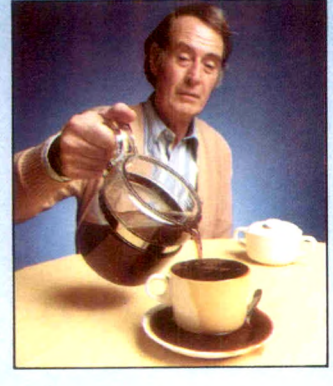
(Also called Hepatic Encephalopathy, Hepatic Coma.)

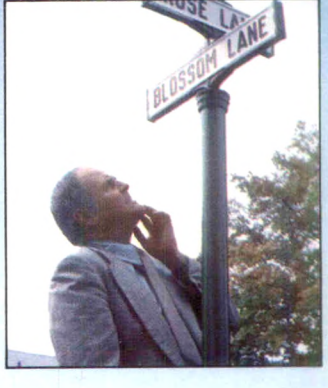












(Please turn page for answer.)

Cephulac®
(lactulose) Syrup

Brief Summary

INDICATIONS: For the prevention and treatment of portal-systemic encephalopathy, including the stages of hepatic pre-coma and coma. Controlled studies have shown that lactulose syrup therapy reduces the blood ammonia levels by 25-50%; this is generally paralleled by an improvement in the patients' mental state and by an improvement in EEG patterns. The clinical response has been observed in about 75% of patients, which is at least as satisfactory as that resulting from neomycin therapy. An increase in patients' protein tolerance is also frequently observed with lactulose therapy. In the treatment of chronic portal-systemic encephalopathy, Cephulac has been given for over 2 years in controlled studies.

CONTRAINDICATIONS: Since Cephulac contains galactose (less than 2.2 g./15 ml.), it is contraindicated in patients who require a low galactose diet.

WARNINGS: *Use in Pregnancy:* Studies in laboratory animals have not revealed a teratogenic potential of lactulose. The safety of lactulose syrup during pregnancy and its effect on the mother or the fetus have not been evaluated in humans. The physician and patient should understand that the possibility that lactulose syrup might cause damage to the human fetus cannot be excluded. Lactulose syrup should not be given during pregnancy unless, in the opinion of the physician, the possible benefits outweigh the possible risks.

PRECAUTIONS: Lactulose syrup contains galactose (less than 2.2 g./15 ml.) and lactose (less than 1.2 g./15 ml.) and it should be used with caution in diabetics. There have been conflicting reports about the concomitant use of neomycin and lactulose syrup. Theoretically, the elimination of certain colonic bacteria by neomycin and possibly other anti-infective agents may interfere with the desired degradation of lactulose and thus prevent the acidification of colonic contents. Thus the status of the lactulose-treated patient should be closely monitored in the event of concomitant oral anti-infective therapy. Other laxatives should not be used especially during the initial phase of therapy for portal-systemic encephalopathy because the loose stools resulting from their use may falsely suggest that adequate Cephulac dosage has been achieved. In the overall management of portal-systemic encephalopathy it should be recognized that there is serious underlying liver disease with complications such as electrolyte disturbance (e.g., hypokalemia) for which other specific therapy may be required.

ADVERSE REACTIONS: Cephulac may produce gaseous distention with flatulence or belching and abdominal discomfort such as cramping in about 20% of patients. Excessive dosage can lead to diarrhea. Nausea and vomiting have been reported infrequently.

DOSAGE AND ADMINISTRATION: The usual dosage is 2 to 3 tablespoonfuls (30 to 45 ml., containing 20 g. to 30 g. of lactulose) three or four times daily. The dosage may be adjusted every day or two to produce 2 or 3 soft stools daily. Hourly doses of 30 to 45 ml. of Cephulac may be used to induce the rapid laxation indicated in the initial phase of the therapy of portal-systemic encephalopathy. When the laxative effect has been achieved, the dose of Cephulac may then be reduced to the recommended daily dose. Improvement in the patient's condition may occur within 24 hours but may not begin before 48 hours or even later. Continuous long-term therapy is indicated to lessen the severity and prevent the recurrence of portal-systemic encephalopathy. The dose of Cephulac for this purpose is the same as the recommended daily dose.

Product Information as of August, 1975

Merrell

MERRELL-NATIONAL LABORATORIES
Division of Richardson-Merrell Inc.
Cincinnati, Ohio 45215, U.S.A.

7-3292(Y366A)

44th Annual
Convention
of the
American College of
Gastroenterology
and
Course in
Postgraduate
Gastroenterology

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The Disneyland Hotel
Anaheim, CA
21-27 October 1979

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For further information
write to:
**American College of
Gastroenterology
299 Broadway
New York, N. Y. 10007**

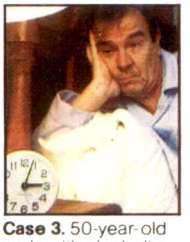
They all do!



Case 1. 53-year-old retired submariner with cirrhosis of uncertain etiology and portacaval shunt



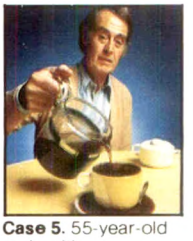
Case 2. 57-year-old widow with primary biliary cirrhosis



Case 3. 50-year-old male with alcoholic cirrhosis



Case 4. 43-year-old salesman with clinically stable Laennec's cirrhosis



Case 5. 55-year-old male with histologically proven cirrhosis



Case 6. 50-year-old male with Laennec's cirrhosis and portacaval shunt

Professional models were used to ensure patient privacy.

Suspect portal-systemic encephalopathy (PSE) in every patient with cirrhosis

Common early symptoms of PSE are:

irritability, euphoria, lack of concern for others, inappropriate behavior, faraway look, inversion of sleep pattern.

Results of recent investigations of PSE:

- Two-thirds of cirrhotic patients with portal hypertension without clinical evidence of PSE revealed impairment of cerebral function on psychometric testing. This dysfunction was in the same range as in patients with brain damage after blunt trauma[1]
- Alcoholic males with cirrhosis demonstrated a mental state significantly inferior to alcoholics without cirrhosis[2]
- The majority of cirrhotic patients with portacaval shunts who appeared mentally normal had demonstrable psychomotor impairment[3]

These inapparent and early stages can last for hours, days, weeks, months or even years. Untreated, they lead to COMA. You can't depend on routine observation to detect PSE.

- Test every cirrhotic for PSE.
- Treat every PSE, regardless of stage.
- Remember, the early stages are the most common; the coma stage is only the tip of the PSE iceberg.

Cephulac (lactulose) Syrup effectively reverses acute and chronic recurrent PSE in over 75% of episodes, without serious adverse reactions, when used as directed.

- lowers blood ammonia levels
- improves mental state
- lessens EEG abnormalities
- permits more normal dietary protein intake
- makes it easier to treat the patient

References:

1. Schomerus, H. and Hamster, W.: Latent portasystemic encephalopathy. Digestion 14:548-549, 1976.
2. Smith, H.H. and Smith, L.S.: WAIS functioning of cirrhotic and non-cirrhotic alcoholics. J. Clin. Psychol. 33:309-313, 1977.
3. Rikkers, L., Jenko, P., Rudman, D. and Freides, D.: Subclinical hepatic encephalopathy: Detection, prevalence, and relationship to nitrogen metabolism. Gastroenterology 72:1119, 1977.

See adjacent page for prescribing information.

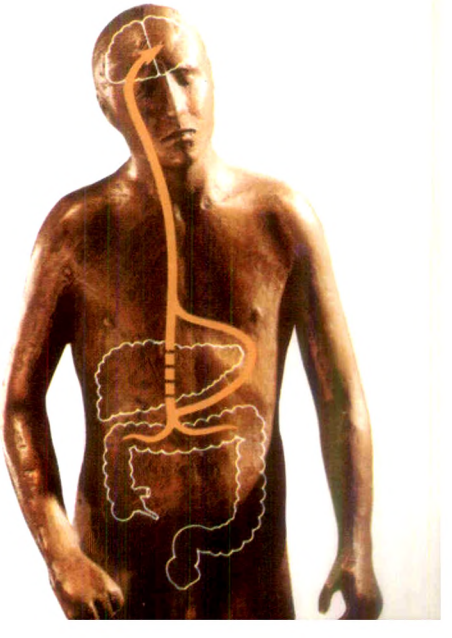
Cephulac®
(lactulose) Syrup

Each 15 ml. of syrup contains: 10 g. lactulose (and less than 2.2 g. galactose, less than 1.2 g. lactose, and 1.2 g. or less of other sugars)

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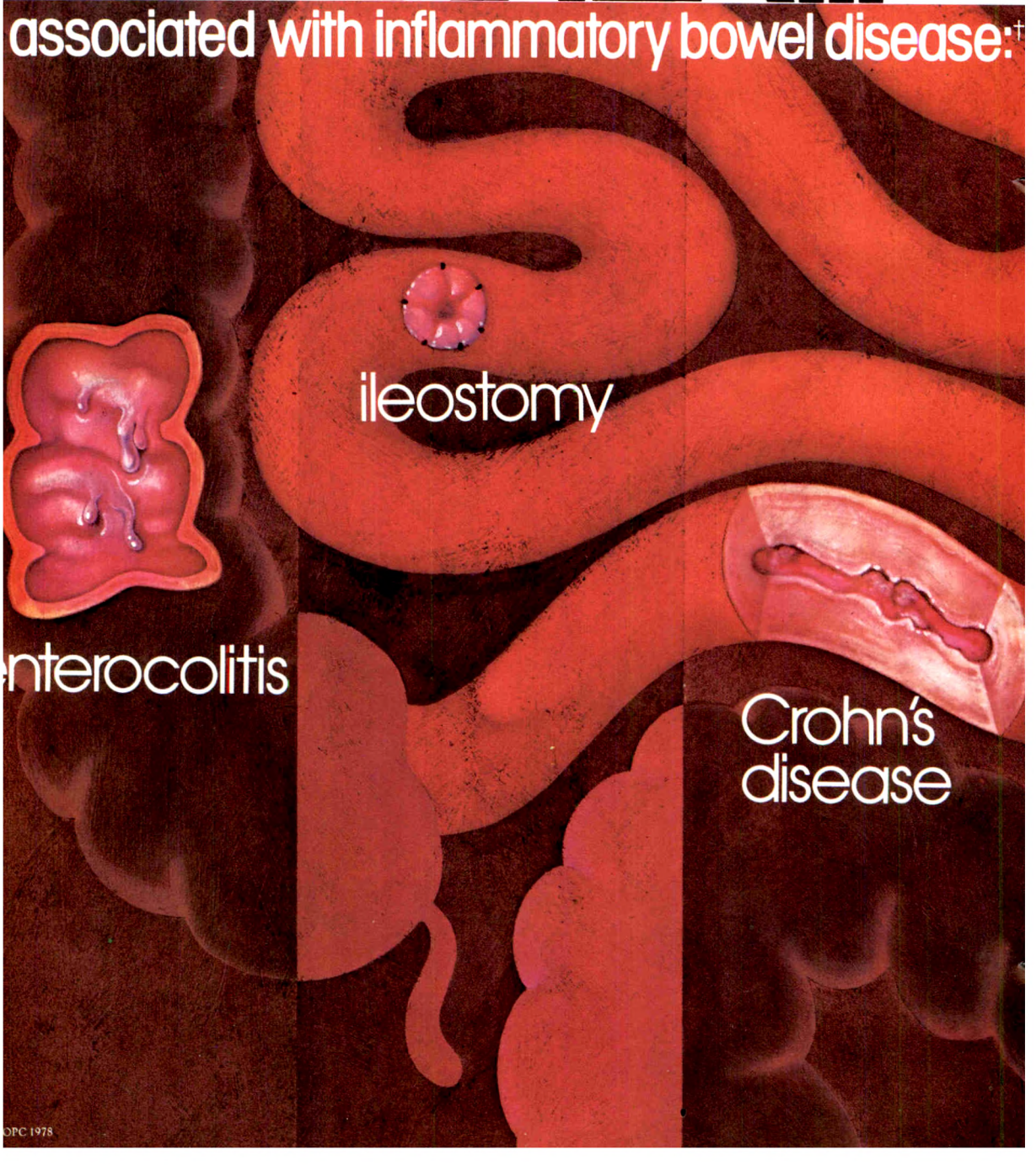
The above advertisement will appear in:
American Journal of Digestive Diseases, American Journal of Gastroenterology, Annals of Internal Medicine, New England Journal of Medicine in 1978



in chronic

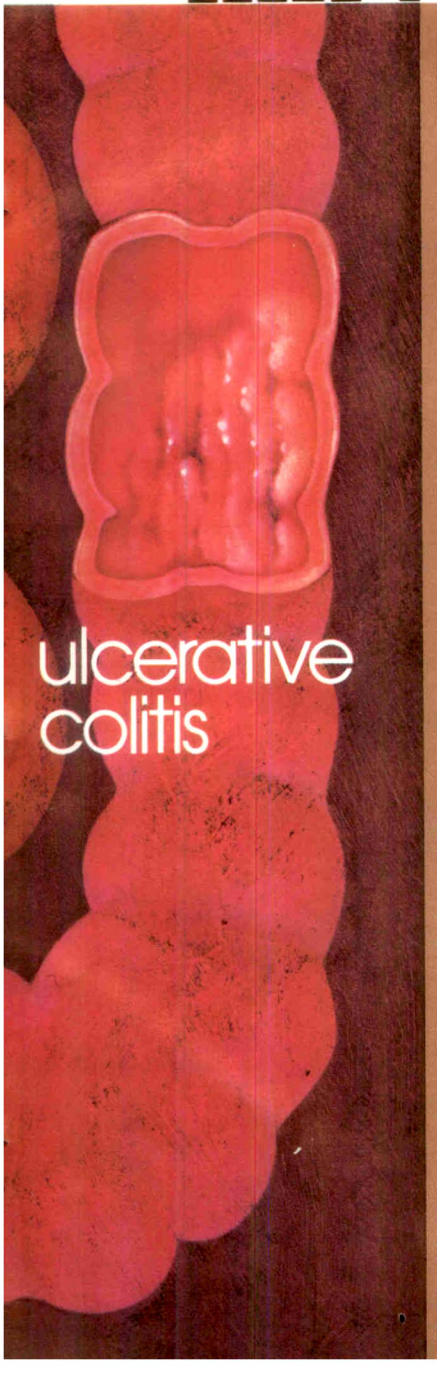
DIARRHEA...

associated with inflammatory bowel disease:†



IMODIUM® CAPSULE

(loperamide HCl)



low incidence of side effects††

IMODIUM is well tolerated—side effects are infrequent, generally of a minor and self-limiting nature, and sometimes difficult to distinguish from the diarrheal syndrome.

compatible with a wide range of medications

In clinical trials exceeding two years, no drug interactions were observed when IMODIUM was used concomitantly with antibiotics, sulfonamides, antihypertensives, barbiturates, corticosteroids and tranquilizers.

no development of tolerance

Tolerance to the antidiarrheal effect of IMODIUM has not been observed to date.

laboratory findings normal in long-term use

No trends toward abnormality were noted in those patients (193 of 358 [54%] with chronic diarrhea) in whom biochemical and hematologic parameters were monitored or in those patients having urinalyses, EKG, and clinical ophthalmologic examinations.

once-daily dosage after titration

The recommended initial dosage is 2 caps *stat*, then 1 capsule after each unformed stool until diarrhea is controlled. Then the daily dosage is reduced to meet individual requirements, and should be given in one single or divided doses.

†Safety and effectiveness in patients under 12 years of age have not been established. Safe use in pregnancy has not been established.

††Please see Prescribing Information on next page.

IMODIUM capsules: an antidiarrheal your patients can stay with

Ortho Pharmaceutical Corporation
Raritan, New Jersey 08869

Effectively controls diarrhea by normalizing stool frequency and consistency...

Significant improvement in bowel function in 21 patients with chronic diarrhea

	Median # stools/day	Median stool consistency	Median # caps/day
Relapse period (drug-free)	**8** (Range: 4-30)	**watery**	—
IMODIUM for 1 month	**2** (Range: 1-8) 75% reduction	**soft**	**4** (Range: 2-8)

..yet effectiveness did not diminish in long-term use

Continued effectiveness of IMODIUM in 18 patients after 6 to 18 months[1]

Median number of stools remained constant: **2/day**

Median stool consistency further improved: **soft to normal**

Median daily dosage remained constant: **4 capsules/day**

in chronic diarrhea associated with inflammatory bowel disease:

IMODIUM® TRADEMARK **Capsules**

(loperamide HCl)

an antidiarrheal the chronic patient can stay with

"Due to its efficacy, rapid onset and long duration of action, lack of long-term drug tolerance, and simple individualized dosage regimen, [IMODIUM] is likely to become one of the commonly used agents for the treatment of chronic diarrhea."[1]

1. Galambos, J.T. et al.: Gastroenterology 70:1026, June 1976.

Ortho Pharmaceutical Corporation
Raritan, New Jersey 08869

OJ 619 R

Brief Summary: Before prescribing, please consult complete prescribing information, a summary of which follows.

DESCRIPTION: IMODIUM (loperamide hydrochloride), 4-(*p*-chlorophenyl)-4-hydroxy-N,N-dimethyl-α,α-diphenyl-1-piperidinebutyramide monohydrochloride, is a synthetic antidiarrheal for oral use.

IMODIUM capsules are classified as a Schedule V controlled substance by federal law (see: Overdosage Section).

CONTRAINDICATIONS: IMODIUM is contraindicated in patients with known hypersensitivity to the drug and in those in whom constipation must be avoided.

WARNINGS: Antiperistaltic agents should not be used in acute diarrhea associated with organisms that penetrate the intestinal mucosa, e.g., toxigenic *E. coli*, *Salmonella*, *Shigella*, and in pseudomembranous colitis associated with broad-spectrum antibiotics.

Fluid and electrolyte depletion may occur in patients who have diarrhea. The use of IMODIUM does not preclude the administration of appropriate fluid and electrolyte therapy. In some patients with acute ulcerative colitis, agents which inhibit intestinal motility or delay intestinal transit time have been reported to induce toxic megacolon. IMODIUM therapy should be discontinued promptly if abdominal distention occurs or if other untoward symptoms develop in patients with acute ulcerative colitis.

PRECAUTIONS: In acute diarrhea, if clinical improvement is not observed in 48 hours, the administration of IMODIUM should be discontinued.

Abuse and Dependence: Physical dependence to IMODIUM in humans has not been observed. However, studies in monkeys demonstrated that loperamide hydrochloride at high doses produced symptoms of physical dependence of the morphine type.

Carcinogenesis: In an 18-month rat study with doses up to 133 times the maximum human dose (on a mg/kg basis) there was no evidence of carcinogenesis.

Pregnancy: Safe use of IMODIUM during pregnancy has not been established. Reproduction studies performed in rats and rabbits with dosage levels up to 30 times the human therapeutic dose did not demonstrate evidence of impaired fertility or harm to the offspring due to IMODIUM. Higher doses impaired maternal and neonate survival, but no dose level up to 30 times the human dose demonstrated teratogenicity. Such experience cannot exclude the possibility of damage to the fetus. IMODIUM should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether IMODIUM is excreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

Pediatric Use: Safety and effectiveness in children have not been established. Therefore, use of IMODIUM is not recommended in the pediatric age group (under the age of 12). In case of accidental ingestion of IMODIUM by children, see Overdosage Section for suggested treatment.

ADVERSE REACTIONS: The adverse effects reported during clinical investigations of IMODIUM are difficult to distinguish from symptoms associated with the diarrheal syndrome. Adverse experiences recorded during clinical studies with IMODIUM were generally of a minor and self-limiting nature. They were more commonly observed during the treatment of chronic diarrhea.

The following patient complaints have been reported: Abdominal pain, distention or discomfort; constipation; drowsiness or dizziness; dry mouth; nausea and vomiting; tiredness.

Hypersensitivity reactions (including skin rash) however, have been reported with IMODIUM use.

IMODIUM Capsule shells contain tartrazine. Allergic reactions have been reported with the ingestion of this dye in some patients.

OVERDOSAGE: Animal pharmacological and toxicological data indicate that overdosage in man may result in constipation, CNS depression, and gastrointestinal irritation. In clinical trials an adult who took three 20 mg doses within a 24-hour period was nauseated after the second dose and vomited after the third dose. If vomiting has occurred spontaneously, a slurry of 100 gm of activated charcoal should be administered orally as soon as fluids can be retained.

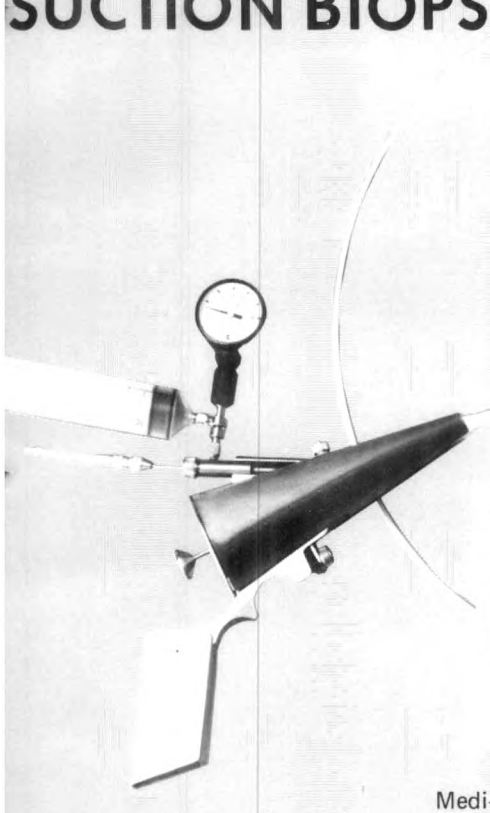
If vomiting has not occurred, gastric lavage should be performed followed by administration of 100 gm of the activated charcoal slurry through the gastric tube. In the event of overdosage, patients should be monitored for signs of CNS depression for at least 24 hours. If CNS depression is observed, naloxone may be administered. If responsive to naloxone, vital signs must be monitored carefully for recurrence of symptoms of drug overdose for at least 24 hours after the last dose of naloxone. In view of the prolonged action of loperamide and the short duration (one to three hours) of naloxone, the patient must be monitored closely and treated repeatedly with naloxone as indicated. Based on the fact that relatively little drug is excreted in urine, forced diuresis is not expected to be effective for IMODIUM overdosage.

HOW SUPPLIED: IMODIUM is available as 2 mg capsules of loperamide hydrochloride. The capsules have a light green body and a dark green cap, with "ORTHO 1000" imprinted on each segment. IMODIUM capsules are supplied in bottles of 100.

IMODIUM (loperamide hydrochloride) is an original product of Janssen Pharmaceutica, Belgium, and co-developed by Ortho Pharmaceutical Corporation. U.S. Patent 3,714,159

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disposable unit-dose
hydrocortisone retention enema

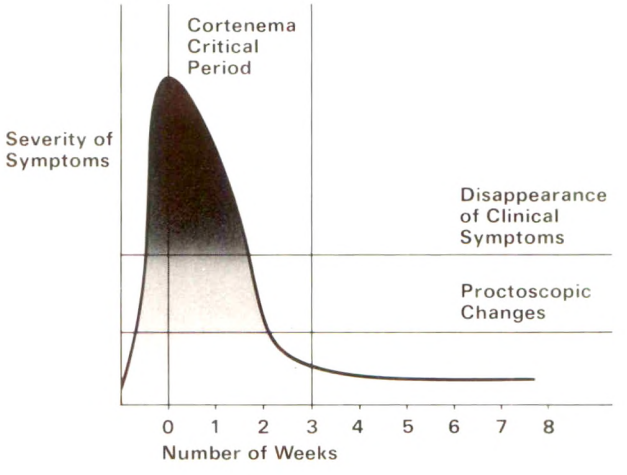
COMPOSITION: Each 60 ml. unit contains Hydrocortisone, 100 mg. in an aqueous solution of carboxypolymethylene, polysorbate 80, and methylparaben, 0.18% as a preservative.
INDICATIONS: Adjunctive therapy in ulcerative colitis; especially distal ulcerative proctitis, proctosigmoiditis, left-sided colitis; proved useful also in some cases involving transverse and ascending colons.
CONTRAINDICATIONS: Systemic fungal infections; recent ileocolostomy.
WARNINGS: In severe ulcerative colitis, avoid delay of needed surgery pending response to medical therapy. Careful insertion of enema tip is advisable to avoid rectal wall damage. Observe warnings of corticosteroid use; increase dosage of rapid-acting corticosteroids in unusual stress; corticosteroids may mask and decrease resistance to infection; prolonged use may predispose to cataracts, glaucoma, secondary ocular infections.
Usage in pregnancy: Pending adequate studies, corticosteroid use in pregnant, lactating or potentially childbearing women requires weighing possible drug benefits against potential hazards to mother and progeny. After large corticosteroid doses during pregnancy, observe neonates for hypoadrenalism.
Hydrocortisone or cortisone therapy may increase blood pressure, sodium and water retention, potassium excretion—effects less likely with synthetic derivatives, except in high doses. Salt restriction and potassium supplementation may be needed. All corticosteroids increase calcium excretion.
Avoid immunization procedures, including smallpox vaccination, during corticosteroid therapy, because of possible neurologic complications and lack of antibody response. Observe corticosteroid-treated patients with latent tuberculosis or tuberculin reactivity for signs of reactivated disease; provide chemoprophylaxis during prolonged corticosteroid dosage.
PRECAUTIONS: Use CORTENEMA cautiously in probability of bowel perforation, abscess or pyogenic infection, new anastomoses, obstruction, extensive fistulas or sinus tracts, and in peptic ulcer, diverticulitis, renal insufficiency, hypertension, osteoporosis and myasthenia gravis. Minimize hazard of adrenocortical insufficiency after prolonged treatment, by reducing dosage gradually and by adding mineralocorticoid and glucocorticoid support in post-treatment stress situations. In surgical infections during corticosteroid therapy, consider increasing antimicrobial dosage.
Use corticosteroids cautiously in hypothyroidism, cirrhosis and ocular herpes simplex; use aspirin cautiously with corticosteroids in hypoprothrombinemia. Psychic derangements may appear and emotional instability or psychotic tendencies may be aggravated with corticosteroid use. Carefully monitor growth of children on long-term corticosteroid therapy. Use the lowest effective corticosteroid dosage and reduce it gradually when possible.
ADVERSE REACTIONS: Local pain of burning, and rectal bleeding attributed to CORTENEMA have been reported rarely. Apparent exacerbations or sensitivity reactions also occur rarely. The following adverse reactions should be kept in mind whenever corticosteroids are given by rectal administration:
Fluid and Electrolyte Disturbances: Sodium retention; fluid retention; congestive heart failure in susceptible patients; potassium loss; hypokalemic alkalosis; hypertension. *Musculoskeletal:* Muscle Weakness; steroid myopathy; loss of muscle mass; osteoporosis; vertebral compression fractures; aseptic necrosis of femoral and humeral heads; pathologic fracture of long bones. *Gastrointestinal:* Peptic ulcer with possible perforation and hemorrhage; pancreatitis; abdominal distention; ulcerative esophagitis. *Dermatologic:* Impaired wound healing; thin fragile skin; petechiae and ecchymoses; facial erythema; increased sweating; may suppress reactions to skin tests. *Neurologic:* Convulsions; increased intracranial pressure with papilledema (pseudo-tumor cerebri) usually after treatment; vertigo; headache. *Endocrine:* Menstrual irregularities; development of Cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetics. *Ophthalmic:* Posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos. *Metabolic:* Negative nitrogen balance due to protein catabolism.
DOSAGE AND ADMINISTRATION: CORTENEMA should be used adjunctively with such supportive measures as dietary control, sedatives, antidiarrheal and antibacterial agents and blood replacement. The usual dosage, administered intrarectally in the evening before retiring, is 1 CORTENEMA per day for 2-3 weeks and every other evening thereafter until clinical and proctologic remission occur. CORTENEMA should be retained at least 1 hour or, preferably, all night and may be facilitated by prior sedative or antidiarrheal medication. Duration of treatment depends on both clinical and proctologic response. Clinical symptoms usually subside within 3-5 days; mucosal improvement may require longer, up to 2-3 months. Discontinue CORTENEMA if improvement fails to occur within 3 weeks.
HOW SUPPLIED: Single-dose 60-cc. bottles, in packages of 1 or 7, with instructions for patients.

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The first three weeks of therapy... that's when you most need:

Cortenema®

disposable unit-dose hydrocortisone retention enema



Once a diagnosis is established, Cortenema often is the only medication required for treatment of mild to moderate distal ulcerative colitis, characterized by rectal bleeding, stool abnormality (diarrhea or constipation), and diffuse mucosal ulceration and friability limited to the rectum or rectosigmoid colon.

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Inflammation, bleeding and tenesmus usually start to subside within three to five days. Sigmoidoscopic examination after two or three weeks will reveal extent of mucosal improvement and direct subsequent therapy. (Severe cases may require up to three months Cortenema treatment followed by gradually reduced doses until discontinuation.)

Patient convenience and economy

Cortenema is unit-dosed, ready to administer, disposable. Available in packages of one or seven.

Hydrocortisone enema therapy provides relief of symptoms and mucosal inflammation with minimal concern for steroid side effects. About 30%-50% absorption may occur, but with only transient adrenal suppression reported. Therapy is economical for the patient. The usual three week course costs far less than even one day of hospitalized treatment.



Originators of hydrocortisone enema therapy.

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See page opposite for brief summary.

LIBRARY

in irritable colon*

When stress makes waves for the spasm reactor...

A normal reaction to emotional stress is a marked increase in both the strength and frequency of wave-like contractions of colonic motility.[1] However, in the patient with irritable bowel syndrome, this psychovisceral reaction is of greater intensity and duration than normal.[2]

The result can be G.I. spasm.

When spasm and pain associated with irritable bowel syndrome call for treatment beyond your counseling and reassurance, Donnatal may prove to be a helpful adjunct. The smooth central sedation and prompt peripheral antispasmodic/anticholinergic action of Donnatal may provide this symptomatic relief necessary to help calm the waves ...and quell the spasm.

References: 1. Almy, T.P., Kern, F., and Tulin, M.: Alterations in colonic function in man under stress. II: Experimental production of sigmoid spasm in healthy persons. *Gastroenterology* 12(3):425-436, 1949. **2.** Almy, T.P., Hinkle, L.E., Berle, B., et al.: Alterations in colonic function in man under stress. III: Experimental production of sigmoid spasm in patients with spastic constipation. *Gastroenterology* 12(3):437-449, 1949.

*Indications: Based on a review of this drug by the NAS/NRC and/or other information, FDA has classified the following indications as possibly effective: adjunctive therapy in the treatment of peptic ulcer; the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

Final classification of the less-than-effective indications requires further investigation.

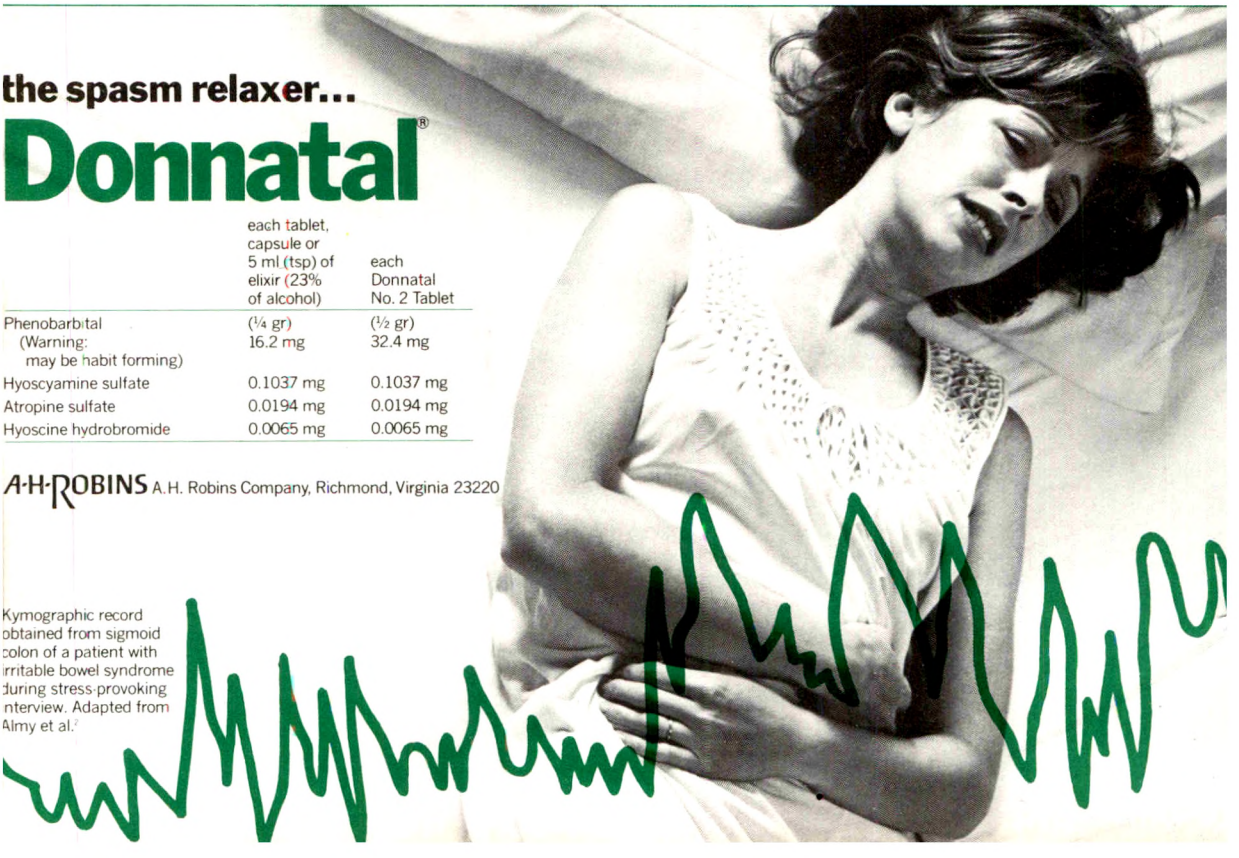
Contraindicated in patients with glaucoma, renal or hepatic disease, obstructive uropathy (for example, bladder neck obstruction due to prostatic hypertrophy), or a hypersensitivity to any of the ingredients. Blurred vision, dry mouth, difficult urination, and flushing or dryness of the skin may occur at higher dosage levels, rarely at the usual dosage.

the spasm relaxer...

Donnatal®

	each tablet, capsule or 5 ml (tsp) of elixir (23% of alcohol)	each Donnatal No. 2 Tablet
Phenobarbital (Warning: may be habit forming)	(¼ gr) 16.2 mg	(½ gr) 32.4 mg
Hyoscyamine sulfate	0.1037 mg	0.1037 mg
Atropine sulfate	0.0194 mg	0.0194 mg
Hyoscine hydrobromide	0.0065 mg	0.0065 mg

A·H·ROBINS A.H. Robins Company, Richmond, Virginia 23220



Kymographic record obtained from sigmoid colon of a patient with irritable bowel syndrome during stress-provoking interview. Adapted from Almy et al.[2]

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FORMERLY THE REVIEW OF GASTROENTEROLOGY

VOLUME 70 DECEMBER, 1978 NUMBER 6

Comparison of the Effects of Glucagon and Atropine Sulfate on Gastric Emptying

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BERNARD D. ROSENAK, M.D.‡
Indianapolis, IN
and
SAMI AHMADZAI, M.D.**
Nengharhar, Afghanistan

Six asymptomatic adult males cooperated in a study of gastric emptying. Each subject was given a test meal of 500 ml. of 3.5% glucose on a fasting stomach. Ten minutes prior to the meal each was given either 1 mg. atropine sulfate, placebo, or 2 mg. glucagon, double-blind and crossover. Each drug was given twice, intravenously, in a random order. The meal was removed by a Salem sump tube half an hour after ingestion.

When compared to placebo, the active drugs significantly ($P < 0.05$) slowed gastric emptying; atropine sulfate was more effective ($P < 0.05$) than glucagon. The active drugs significantly ($P < 0.05$) decreased total gastric acid secretion and total gastric chloride as compared to placebo. Glucagon significantly ($P < 0.05$) increased the blood glucose concentration as compared to placebo.

These results indicate that both glucagon and atropine sulfate slow the gastric emptying of a liquid sugar meal from the stomach.

Work was done at Wishard Hospital, Lilly Laboratories for Clinical Research and Indiana University School of Medicine.

* Lilly Laboratories for Clinical Research; Associate Clinical Professor of Medicine, Indiana University School of Medicine.

† Lilly Laboratories for Clinical Research; Instructor, School of Business, Butler University.

‡ Clinical Professor of Medicine, Indiana University School of Medicine; Consultant in Gastroenterology, Lilly Laboratories for Clinical Research.

** Formerly Fellow, Lilly Laboratories for Clinical Research; currently, Jalalabad University Hospital, Nengharhar.

INTRODUCTION

The fundus of the stomach acts as a reservoir and the antrum as a metering pump which controls the rate of transfer of material from the stomach to the duodenum.[1] Since both anticholinergics and glucagon inhibit gastric motility, they would both be expected to slow gastric emptying.[2-5] This study was undertaken to compare the effects of glucagon and atropine sulfate on gastric emptying.

Method

Six cooperative asymptomatic adult males, ranging in age from 26-60 years with an average age of 46 years, were hospitalized for this study. Each subject was informed and a signed consent was obtained. The study was reviewed and approved by the Lilly Clinic institutional review committee.

All subjects were fasting on the morning of the test. They were not on any drugs for 48 hours prior to or at any time during the study. No food had been taken after dinner the previous evening and smoking was not allowed on the morning of the test. Prior to starting, each subject was questioned concerning symptoms and pulse and blood pressure were measured and recorded. A #12 French Salem sump tube was passed and the stomach emptied. Blood was obtained for a fasting blood glucose and serum potassium.

Medications included placebo (diluting solution for glucagon), glucagon 2 mg. and atropine sulfate 1 mg. All medications were given intravenously, double-blind and crossover. The medications were given according to a random block design at not less than 48-hour intervals. Only one drug was given on any one test day. Each medication was given twice in a randomized manner. Ten minutes after the medication was given, 500 ml. of the test meal was administered. The test meal contained 17.5 gm. of sucrose and 30 mg. of phenol red in 500 ml. of distilled water. Subjects were asked to drink the test meal as rapidly as possible.

Throughout the test all subjects remained seated. They were asked to expectorate all saliva into an emesis basin. One-half hour after the drug was given, the pulse and blood pressure were measured and blood was obtained for glucose and serum potassium analysis. The subjects were questioned again concerning dryness of the mouth, headache, nausea, vomiting and abdominal distress. If a positive answer was obtained, the subject was asked to quantitate the symptom according to a score of 1-4 (1-mild, 2-moderate, 3-moderately severe and 4-severe). All data and responses were recorded on a standard form.

One-half hour after instillation of the meal, the subject was asked to lie on his left side and the meal remaining in his stomach was removed. The total volume removed was recorded. When no more meal could be removed, the subject was asked to drink 200 ml. of water and the stomach was completely aspirated again. The total volume of this specimen was recorded. Samples obtained consisted of: 1. a 20 ml. sample of original meal; 2. a 20 ml. sample of removed meal and 3. a 20 ml. sample of wash water. The two gastric samples obtained at the end of the study were filtered through glass wool and the filtrate analyzed for the concentration of phenol red.

The absorbance of the original meal, recovered sample and washings was determined at 540 mμ with a Gilford spectrophotometer. The absolute amount of phenol red was used to estimate the portion of meal remaining in the stomach. The dilution of phenol red was used as an estimate of the quantity of gastric secretion during this time period. The method of calculating the quantity of meal remaining in the stomach and gastric secretion during the test period follows:[1]

Let C_0 equal the initial concentration of phenol red in the 500 ml. meal; C_1, the concentration of phenol red in the gastric aspiration extracted after ½ hour; C_2, the concentration of phenol red in the aspirate recovered after the 200-ml. water washing; V_E, the volume of material aspirated at

TABLE I

THE AVERAGE OF THE VALUES FOR THE SIX MEN GIVEN EACH DRUG TWICE

Parameters of measure	Placebo	Glucagon 2 mg.	Atropine sulfate 1 mg.
Gastric contents			
Vol. of meal in ml.	79.2	140.0*	202.5*†
ml. secretions	67.4	105.3	66.9
Final pH	3.1	3.4	3.5
Total HCl mEq.	37.5	15.9*	7.1*
Total chloride mEq.	69.1	44.5*	22.4*†
Total sodium mEq.	25.0	20.1	11.6*
Blood or serum			
Glucose before mg.%	77.4	78.6	76.1
Glucose after mg.%	106.3	130.3*	88.0
Potassium before mEq./l.	4.5	4.6	4.6
Potassium after mEq./l.	4.4	4.1	4.5
Measurements			
Pulse before	81	83	83
Pulse after	77	82	96 *†

* Drug vs. placebo $P < 0.05$
† Atropine sulfate vs. glucagon $P < 0.05$

½ hour; V_R, the volume of material remaining in stomach at the ½ hour, including that obtained with the 200 ml. of wash water; and V_{RT}, the total volume of meal remaining in stomach after ½ hour (assuming no secretions).

Then an estimate of V_R (V_R) is obtained by

$$V_R = \frac{(200)\ (C_1)}{C_1 - C_2}$$

and an estimate of V_{RT} (V_{RT}) is obtained by

$$V_{RT} = \frac{(C_1)\ (V_E) + (C_2)\ (V_R)}{C_O}$$

An estimate of secretion (S) obtained by

$$S = V_E + (V_R - 200)\ V_{RT}$$

As an illustration, let $C_O = 0.060$; $C_1 = 0.045$; $C_2 = 0.006$ and $V_E = 232$ cc.

Then

$$V_R = \frac{(200)\ (0.045)}{0.045 - 0.006} = \frac{9.0}{0.039} = 230.76 \approx 231$$

$$V_{RT} = \frac{(0.045)\ (232) + (0.006)\ (231)}{0.060} = 197.1 \approx 197$$

Then $S = 232 + (231 - 200) - 197 =$ 66 ml. of secretion.

The filtrate of all three samples was used to determine the pH, titratable acid, sodium, and chloride. The pH was determined with a pH meter (Radiometer, Copenhagen, Denmark). A. 0.1 N NaOH solution was used to measure the titratable acidity. Samples were titrated to pH 7. Sodium was obtained by AutoAnalyzer

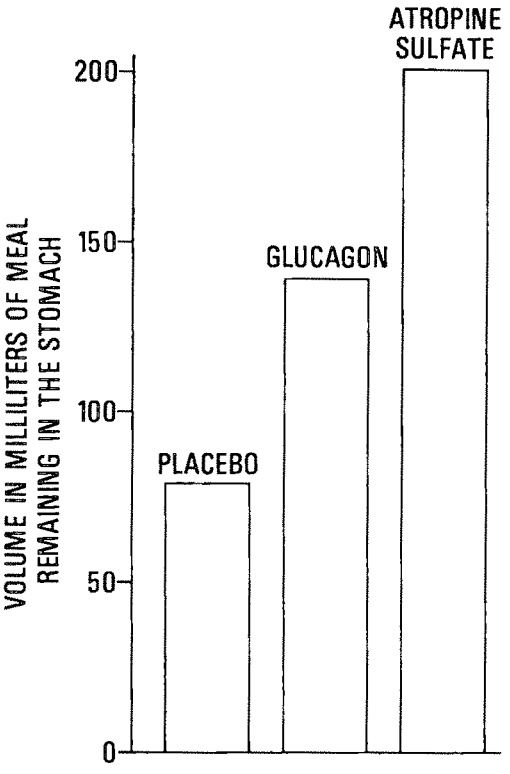


Fig. 1—The average volume of meal remaining in the stomach one-half hour after medicaton administraton.

flame photometer and chloride by the standard chloridometer procedure.

Results

When evaluating the data obtained from these studies, certain assumptions were made. These are as follows: 1. The pattern on gastric emptying is exponential in form; 2. dilution of marker was caused by "secretion" and none of it was from saliva or duodenal contents, 3. gastric secretion was relatively constant during the study period; 4. mixing of secretions and the material in the stomach occurred and 5. each sample was representative of the specimen from which it was obtained.

The average of the values for the calculated volume of meal in ml. remaining in the stomach, ml. of secretions, total HCl in mEq., final pH of meal; total chloride in mEq., total sodium in mEq., blood glucose in mg.% and serum potassium in mEq./l. are presented in Table I. One subject secreted no acid. To determine the effect the meal and drugs had on gastric secretion of HCl, the average for the pH and total acid for five subjects was calculated. A graphic representation of the volume of meal remaining in the stomach is presented in Figure 1.

The data were evaluated by an analysis of variance. Duncan's multiple range tests were used to compare treatment effects to each other. The calculated volume of meal remaining in the stomach was used as the measure of drug effect on gastric emptying, assuming no secretions during the period of the test. A summary of the results is presented in Table I. When the active agents were compared to placebo, both drugs effectively slowed ($P < 0.05$) gastric emptying and atropine sulfate was significantly ($P < 0.05$) more effective than glucagon.

When compared to placebo, both active drugs significantly ($P < 0.05$) decreased the total acid secreted and total gastric chloride.

When glucagon was compared to placebo, there was a significant ($P < 0.05$) increase in the blood glucose concentration. Considering the actions of glucagon, this is not unexpected.

Although the average blood glucose concentration was lower after atropine sulfate than after placebo, the difference was not significant. Sugar is not absorbed from the stomach. One would expect a drug that slows gastric emptying will prevent the sugar meal from leaving the stomach, allowing less to pass into the small bowel to be absorbed. Emptying of the sugar meal was slowed after atropine sulfate; thus, the

TABLE II

THE TOTAL NUMBER AND INTENSITY OF REPORTS OF SIDE EFFECTS IN THE SIX SUBJECTS GIVEN EACH DRUG TWICE

	Placebo		Glucagon 2 mg.		Atropine sulfate 1 mg.	
	No. of reports	Intensity	No. of reports	Intensity	No. of reports	Intensity
Nausea	0	0	5	12	0	0
Vomiting	0	0	2	2	0	0
Headache	0	0	1	1	1	1
Dryness of the mouth	1	2	0	0	5	7
Blurring of vision	0	0	0	0	1	1
Total number	1		8		7	
Total intensity		2		15		9

average blood glucose concentration was less after atropine sulfate than after placebo administration but the difference was not significant. When atropine sulfate was given, the average gastric sodium concentration was less ($P < 0.05$) than after placebo.

There was no significant difference between the treatments in measures of volume of gastric secretion or final pH.

The pulse and blood pressure were measured immediately before and 30 minutes after the drug was given. The results are summarized in Tables I and II. After atropine sulfate there was a significant ($P < 0.05$) increase in the pulse rate as compared to the initial value obtained that day. There were no significant changes in the pulse rate or blood pressure after glucagon was given. When placebo was given, there was one report of dryness of the mouth with a total score of 2; when glucagon was given, there were five reports of nausea, two of vomiting and one of headache, for a total score of 15. After atropine sulfate, there were five reports of dryness of the mouth and one each of headache and blurring of vision for a total score of 9.

COMMENT

In a similar study of gastric emptying, the present authors compared 0.5 mg. and 1 mg. of atropine sulfate to 1 mg. and 2 mg. of glucagon and to placebo. The same meal as given in this study was used. The subjects were given a capsule containing 325 mg. of potassium iodide and the time of appearance of iodine in the saliva was determined. The use of potassium iodide was developed as a simple measure of drug effect on gastric emptying.[2] In that study, the meal was removed in one hour. The results indicated that when the volume of the meal remaining in the stomach was determined, a dose response was not demonstrable for either drug. There was a significant ($P < 0.05$) slowing of emptying of the meal when atropine sulfate was compared to glucagon. When time of appearance of potassium iodide in the saliva was measured, there was a significant dose response for atropine sulfate ($P < 0.001$) and for

glucagon ($P < 0.005$) and both active drugs significantly ($P < 0.001$) slowed gastric emptying as compared to placebo. These results indicate that when studying short acting drugs such as glucagon, one may not show a response using the Hunt and Knox[1] technic unless the meal is removed at fractional time periods.

A feeling of nausea and or vomiting may slow gastric emptying. In this study when the initial blood samples were obtained medication was given and a Salem sump tube was promptly passed into the stomach to remove any gastric contents. Feelings of nausea and or vomiting occurred with passage of the tube and were gone in two to three minutes. Obviously if any significant nausea and or vomiting occurred the subjects could not have taken the meal orally or have retained it. Glucagon is known to cause nausea and or vomiting. The authors believe that the passage of the tube most probably stimulated these symptoms. All volunteers were free of symptoms shortly after passage of the tube. None had nausea and or vomiting prior to or after drinking the meal.

It is thought that antral peristaltic contraction is the major mechanism controlling gastric emptying. Stemper and Cooke[6] continuously monitored antral peristalsis and the gastric emptying of a liquid test meal. They reported that the rate of gastric emptying was related to the force and frequency of antral contractions. They noted however, that significant emptying occurre in the absence of contractions and tha forceful contraction was sometimes associ ated with negligible emptying. They con cluded that the antrum plays a significan role in gastric emptying but that other un defined forces may be operative.

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Alcohol-induced Gastric and Duodenal Lesions in Man*

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To determine the effect of an acute dose of ethanol on the stomach and duodenum, seven alcoholic subjects with previously normal upper gastrointestinal endoscopy were reevaluated with endoscopy and directed biopsy three hours after the oral ingestion of ethanol (1 gm./kg. body weight) as a 35 gm./100 ml. solution. After ingestion of alcohol, all seven subjects had moderate to severe antral erythema and friability and two had patchy erosions and hemorrhage in the antrum and fundus of the stomach. Five of seven subjects had changes in the duodenal bulb consisting of erythema similar to that in the antrum of the stomach. Microscopically, after alcohol, four of seven demonstrated focal subepithelial hemorrhage and another had frank mucosal hemorrhage in the antrum. In the duodenal bulb, four of seven subjects demonstrated focal subepithelial hemorrhage in the tips of bulbar villi and four of seven had striking infiltration of eosinophils in the subepithelial stroma. These histologic alterations were not present in prealcohol biopsies or in biopsies in two additional subjects given club soda alone or beef bouillon, or in repeat biopsies in two subjects re-endoscoped three days after the ingestion of alcohol when the endoscopic findings were again normal. It is concluded that a single dose of alcohol consistently causes macroscopic and microscopic antral and duodenal alterations.

Introduction

Endoscopic evidence of gastric and duodenal inflammation after excessive alcohol ingestion has often been described[1, 2] and we and others have noted histologic changes consisting of focal areas of subepithelial hemorrhage and increased numbers of eosinophils in the *lamina propria* in patients with a high prevalence of alcohol abuse.[2-5] The fact that blind biopsies of the distal duodenum following alcohol intoxication have not revealed any histologic abnormalities has often been cited as evidence against a causal relationship between alcohol and duodenitis.[6] Reports in both man and rats indicate, however, that when lesions occur, they are located in the proximal duodenum, are patchy and rather short-lived.[1, 7, 8] In this controlled study, fiberoptic panendoscopy and directed biopsy were used to assess the effects of a single dose of alcohol on the stomach and proximal duodenum.

Methods

Seven male alcoholic volunteers, ranging in age from 37 to 52 years, were selected from the Gastrointestinal-Liver Service of the Bronx Veterans Administration

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* Read before the Annual Meeting of the American Gastroenterological Association, Miami, FL, 27 May 1976.

TABLE I

ENDOSCOPIC AND HISTOLOGIC CHANGES IN THE STOMACH AND DUODENAL BULB IN SEVEN SUBJECTS STUDIED THREE HOURS AFTER THE INGESTION OF 1 GM./KG. ETHANOL (35% V/V)

Subject	1	2	3	4	5	6	7
Endoscopic changes							
None	D	D					
Erythema and friability	S		D	S/D	S/D	S	
With hemorrhage or petechiae		S				D	S/D
Histologic changes							
Eosinophilla in *lamina propria*	S/D	S/D	S	S	D		D
Subepithelial hemorrhage		S	S	S/D	S/D	D	D

S=Stomach, D=Duodenum, S/D=Stomach and Duodenum

Hospital, after they had undergone upper gastrointestinal endoscopy with gastric and duodenal biopsy in the course of their hospitalization. All patients gave informed consent to this study which was authorized by the Review Committee on Human Studies of the Bronx Veterans Administration Hospital. Patients were considered to be alcoholic if their history included ethanol ingestion of at least 2.5 gm./kg./day for a period of not less than one month prior to hospitalization. Most patients were admitted for complications of alcohol abuse. Patients with endoscopic evidence of gastric or duodenal inflammation or those with a history of gastrointestinal bleeding, gastric or duodenal ulcer disease, bleeding diathesis, or ingestion of drugs known to affect the gastric mucosa were excluded from the study. In addition, patients with evidence of active liver disease or jaundice were also not considered.

After a period of alcohol abstention of not less than two weeks on a standard hospital diet and not less than 72 hours after the first endoscopy, subjects were kept fasting for 12 hours and then given ethanol, 1 gm./kg. body weight, diluted to a 35 gm./100 ml. solution in club soda equivalent to 6-7 ounces of an 86 proof beverage. Patients consumed the alcohol at their own pace over a total time varying from 20-30 minutes. Three hours following alcohol ingestion, venous blood was drawn for the measurement of alcohol levels (by the alcohol dehydrogenase method[9]), the subjects were premedicated with diazepam (5-10 mg intravenously) and endoscopy was performed with an Olympus GIFD 2 panendoscope. The gastric and duodenal mucosa were evaluated by the same two observers using an arbitrary division of moderate to severe erythema with friability with or without evidence of gross mucosal hemorrhage or petechiae. Except for friability which was defined as bleeding upon contact with the endoscope, the lesions were assessed before the endoscope had entered a given region to avoid damage caused by the endoscopy. Photographic



Fig. 1—Subepithelial hemorrhage in the gastric antrum three hours after the ingestion of 35% ethanol (1 gm./kg.). The subepithelial *lamina propria* is filled with extravasated red blood cells (Hematoxylin and eosin, original magnification x400).

documentation was obtained. Biopsies were taken from affected areas of the stomach and duodenum after alcohol or from the antrum and duodenal bulb during the pre-alcohol endoscopic examination. Biopsy specimens were fixed in buffered formalin, stained with hematoxylin and eosin, or with toluidine blue. Pre- and postalcohol biopsies were coded, paired for each patient and read by light microscopy by one pathologist experienced in examining small intestinal mucosa, without knowledge of the endoscopic findings. Two additional subjects were re-endoscoped three days after the control endoscopy and three hours

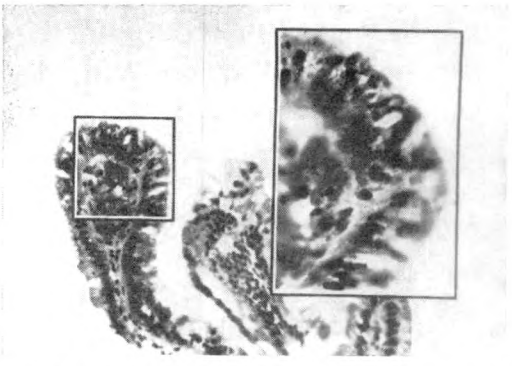


Fig. 2—Subepithelial villus hemorrhage in the duodenal bulb. The subepithelial *lamina propria* contains extravasated red blood cells (Hematoxylin and eosin, original magnification x250). *Insert*: higher magnification showing the hemorrhage breaking through the villus epithelium (Hematoxylin and eosin, original magnification x400).

following the ingestion of club soda alone or another gastric stimulant, beef bouillon. Two subjects were re-endoscoped three days after the ingestion of alcohol to evaluate the extent of healing of previously observed lesions. Biopsies were obtained and handled as described previously.

Results

Prealcohol:—In all seven subjects, no endoscopic abnormalities of the mucosa of the stomach, duodenal bulb or descending duodenum were seen. The mucosa of the stomach was uniformly orange-red in color and glistening. There was no evidence of erosion, erythema or opaque mucus covering. The normal duodenal bulb was considered to have a similarly smooth, glistening mucosa with a characteristic "feathery" appearance of the mucosa.

Postalcohol:—The mean (± SEM) venous alcohol level three hours after alcohol ingestion was 197 ± 15 mg./100 ml. At this time, all seven subjects had changes in the antrum of the stomach varying from a mottled erythema to diffuse erythema with

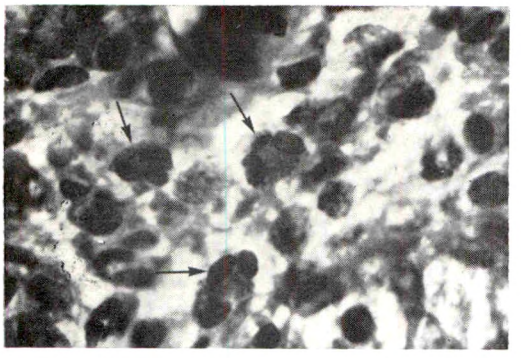


Fig. 3—High power magnification of an area of subepithelial *lamina propria* in the duodenal bulb showing several granular, bilobed eosinophils (arrows) in a single field (Hematoxylin and eosin, original magnification x1,000).

friability. The changes tended to be maximal near the pylorus. In addition, two patients had multiple areas of patchy erosion and hemorrhage predominantly in the body of the stomach (Table I).

In five of seven subjects given alcohol, the mucosa of the duodenal bulb revealed changes similar to those in the antrum of the stomach. The mucosa varied from a mottled, granular erythema to diffuse erythema and friability. In the two individuals with the most severe lesions, several petechiae were seen. In three of the subjects the erythema did not extend beyond the apex of the bulb while in the fourth there was patchy erythema extending about 5 cm. into the proximal duodenum. Three days after alcohol, and also following club soda or beef bouillon, the endoscopic appearance of the mucosa of both stomach and duodenum was normal.

Histology:—Biopsy specimens taken from the affected areas of the stomach revealed hemorrhage into the subepithelial *lamina propria* in four of the seven subjects. The hemorrhage tended to occupy the area just below the epithelium, between the gastric glands (Fig. 1) and occasionally broke through the epithelium.

In the duodenal bulb, hemorrhage was seen in the subepithelium of the tips of villi in four of seven patients. The hemorrhage was occasionally noted to break through the villus tip (Fig. 2). Large numbers of eosinophilic cells were observed in the subepithelial *lamina propria* (Fig. 3), often as many as 20 to 40/low power field (x250). Most were typical bilobed eosinophils but others were mononuclear. Staining with toludine was negative for the presence of mast cells, which usually stain metachromatically.

Microscopic examination of biopsies obtained prior to the alcohol administration and three days thereafter showed varying numbers of lymphocytes and plasma cells in the *lamina propria* and occasional eosinophils but no specimen revealed subepithelial hemorrhage or more than occasional eosinophils in either stomach or duodenum.

Comment

This study demonstrates that a single dose of alcohol in an amount similar to that ingested by our alcoholic population causes a consistent macroscopic lesion in the stomach and proximal duodenum which is often accompanied by microscopic evidence of subepithelial hemorrhage and/or infiltration of the subepithelial *lamina propria* by eosinophils.

Alcohol has been associated with acute gastritis since William Beaumont's classic studies of his patient Alexis St. Martin. He noted mucosal erythema, superficial erosions and cloudy viscid secretion after each of St. Martin's alcoholic sprees.[10] Palmer was able to demonstrate similar gastric mucosal inflammatory changes after severe alcohol intoxication of varying duration in young men, which healed in seven to 20 days.[11] There is evidence that there is an increased incidence of chronic gastritis in

alcoholics.[12] There is little experimental evidence, however, that ingestion of ethanol alone causes acute gastric mucosal hemorrhage in man.[13] Davenport showed that ethanol in concentrations greater than 14% breaks the gastric mucosal barrier in dogs but studies of chromium tagged red blood cells have failed to demonstrate increased fecal blood loss after ethanol in man.[14, 15] Our observations clearly demonstrate that an acute dose of ethanol, insufficient to produce intoxication in our subjects, can cause what Palmer has described as the earliest lesion of hemorrhagic gastritis.[7]

The duodenum and proximal small intestine are exposed to high concentrations of alcohol, as high as 4 gm./100 ml. after ingestion of a 25% solution.[16] Duodenitis characterized by mucosal erythema, friability and hemorrhage have been concomitants of alcohol abuse but other factors such as other illnesses or drug ingestion have often been associated[1, 2] and a causal effect has not been demonstrated. In the rat, the acute intragastric administration of ethanol produces patchy hemorrhagic erosions in the proximal small intestine which are well defined after one hour and may be resolved after 16 hours.[7] In this study, the lesions produced by alcohol were often patchy, seldom extended beyond the duodenal bulb and disappeared within three days. Other endoscopic reports of nonspecific duodenitis have described similar findings.[1, 8] Thus, it is not surprising that previous attempts to demonstrate alcohol induced damage by blind distal biopsy of the distal duodenum have been unsuccessful.[6]

Histologically, the duodenal lesion after alcohol consists of subepithelial villus hemorrhage and/or infiltration of eosinophils. It is unlikely that this type of subepithelial hemorrhage represents trauma caused by the endoscope. Intramural hemorrhage in the superficial layers of the gastric or duodenal mucosa may be interpreted by the pathologist as an artifact.[2] It is doubtful, however, that this is the case when specimens are obtained from areas of obvious erythema or hemorrhage. Indeed, in our subjects, intramural hemorrhage was seen only in biopsies taken from endoscopically abnormal areas clearly away from previous biopsy sites and in none of seven control biopsies, nor in a total of four subjects endoscoped three days after the control endoscopy without the ingestion of alcohol. Thus, trauma from the previous endoscopy could not be demonstrated to cause these changes. This type of lesion has been previously noted in the stomach where it has been called the earliest lesion of hemorrhagic gastritis[10] and it seems that this represents the duodenal counterpart of the gastric lesion.

The cellular reaction found in our subjects showed a striking preponderance of eosinophils. Eosinophils have been noted previously in biopsies from patients with duodenitis.[2-4] In an extensive evaluation, however, of 51 patients with duodenitis, Cotton was able to find mucosal eosinophilia in only three patients (6%) but the relationship to alcohol was not specified.[5]

We conclude that alcohol in amounts commonly ingested acutely by alcoholics is capable of inducing macroscopic and microscopic alterations in the stomach and duodenum. Our study clearly implicates alcohol as an etiologic factor of duodenitis.

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Cholecystokinin Cholecystography in the Diagnosis of Acalculous Extrahepatic Biliary Tract Disorders

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Cholecystokinin cholecystography represents a study designed to identify patients with acalculous extrahepatic biliary tract disorders. In this study, a positive cholecystokinin cholecystogram (CCK-GB) was defined as both reproduction of the patient's biliary tract-type pain plus one or more of various roentgen abnormalities. Using these criteria, 20 patients had a positive CCK-GB. After failure of medical management, 19 of these patients came to surgery. Seventeen of 18 available for follow-up were cured of their biliary tract pain by surgery. Follow-up of this group of patients has ranged from one month to 60 months. In view of our findings plus those in other reported series, we conclude that CCK-GB provides a reliable study for the diagnosis of acalculous extrahepatic biliary tract disorders.

The patient with a history consistent with biliary tract-type pain and a normal oral cholecystogram is not infrequently seen in a clinical gastroenterology practice. Such patients carry many different labels—gastroenterologic, nongastroenterologic and even psychiatric—although it is clear that their symptoms are emanating from the biliary tract. The pain in these cases is not due to calculous disease but rather, in most cases, to a motor disorder in the biliary tract. Cholecystokinin cholecystography (CCK-GB) represents a study designed to identify such patients. This paper records the experience with 29 CCK-GBs performed at United Hospital between September, 1971 and August, 1976.

Material and Methods

The United Hospital Research Committee approved this study, and written informed consent was obtained from each patient. Twenty-nine patients with biliary tract-type pain and at least one normal oral cholecystogram were studied. The study group included 25 females and four males with ages ranging from 17-81 years. Duration of symptoms varied from two months to approximately 30 years. In addition to at least one normal oral cholecystogram, most patients also had noncontributory upper gastrointestinal and small bowel series, barium enemas and intravenous pyelograms.

For CCK-GB, the patients were given 4 gm. (8 tablets) of Telepaque® (iopanoic acid) following a fat-free meal the evening before. The next day an intravenous infusion of normal saline was started. Roentgenograms of the gallbladder were taken with the patient in the left prone oblique position. Then, without the patient's knowledge, 1.5 Ivy units of CCK/kg. of body weight was injected over a three-minute

From the Departments of Medicine, Radiology and Pathology, United Hospital.

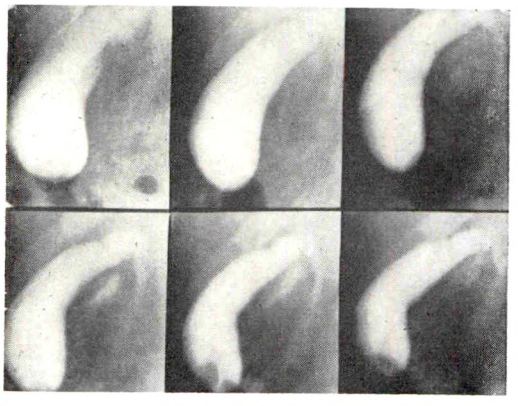


Fig. 1—Normal gallbladder response to a three-minute infusion of CCK (1.5 Ivy units/kg.) *Top*: 2, 4, 6; *bottom*: 8, 10, 20 minutes postinfusion. Progressive emptying of the gallbladder. Excellent ductal visualization. Note filling of the duodenal bulb at eight minutes. No abnormal contractions occur including the site of a septum near the infundibulum.

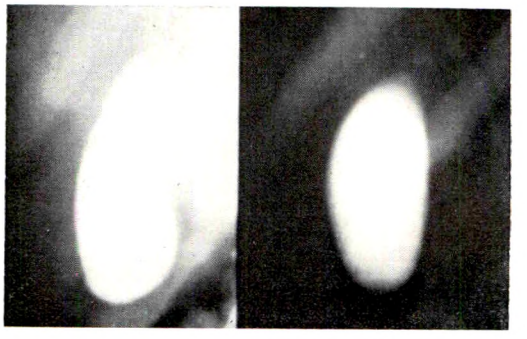


Fig. 2—Spasm of the gallbladder neck. *Left*: Normal slender resting gallbladder. *Right*: Eight minutes post-CCK infusion. Gallbladder assumes ovoid shape with tapering of neck. Minimal emptying. Poor duct visulization.

period through the I.V. tubing. The CCK was obtained from the GIH Research Unit, Chemistry Department, Karolinska Institutet, Stockholm, Sweden. Films were taken 2, 4, 6, 8, 10, 20, and 30 minutes postinfusion.

During the entire 30-minute study period, one of the authors (M.N.) remained with the patient, recording any symptoms experienced. Potential symptoms were not mentioned to the patient before or during the CCK-GB. Patients were only told that CCK-GB is a test designed to evaluate gallbladder function. Two types of symptoms were encountered. During the three minutes of the CCK infusion, almost all patients complained of nausea and crampy periumbilical pain. This has been attributed to CCK stimulation of the small bowel and the sigmoid colon.[1, 2] During the first 10 minutes of the study but typically after the aforementioned symptoms, some patients complained of pain simulating precisely in location but not necessarily in intensity the type of discomfort which led to the CCK-GB. This has been labeled biliary tract-type pain.

Roentgenograms were examined after completion of the CCK-GB. Normal radiographic responses to CCK are as follows, (Fig. 1):

Gallbladder:—During the first two minutes, there is generalized contraction, filling the cystic and common bile ducts. This is followed by a relative hypercontraction of the gallbladder neck, during which there may be little emptying. Should hypercontraction of the neck occur, it should not last beyond five minutes. The neck then relaxes, and emptying again ensues, continuing for another 10-15 minutes. At this point, relaxation occurs and refilling begins. Evacuation averages 38%[3] with a range from 7-60%. There should be no persistent areas of spasm. The gallbladder generally assumes a more slender shape. Individual configuration is so variable, however, that, in the absence of focal spasm, over all change in shape is usually of no significance.

Ductal system:—The common duct should be well-visualized and show no areas of narrowing. Visualization of the common hepatic duct is variable. The spe-

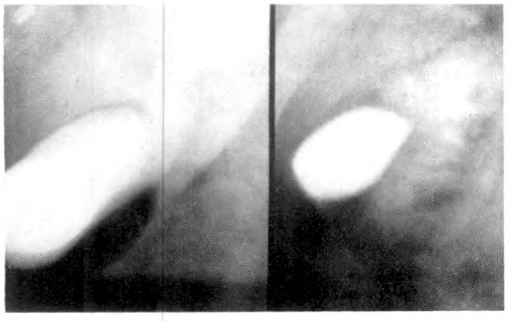


Fig. 3—Spasm of the body and fundus. *Left*: Resting gallbladder. A septum divides the body near the infundibulum. The fundus is folded upon the body. *Right:* Eight minutes post-CCK infusion. Spasm with tapering has occurred at the level of the septum. A minute hypercontracted fundus is evident.

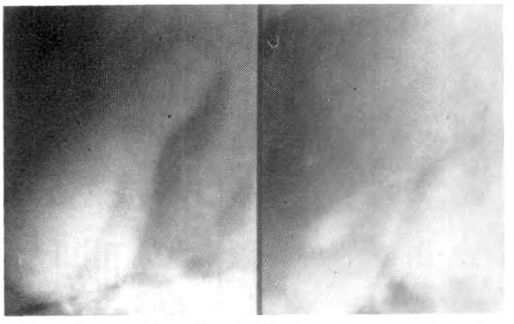


Fig. 4.—Generalized gallbladder hypercontraction. *Left*: Normal resting state. *Right*: Six minutes post-CCK infusion. Almost complete emptying has occurred. The gallbladder is string-like in configuration.

cific gravity of concentrated opacified bile is greater than liver bile so that reflux may easily occur into the dependent common hepatic duct.[4] This results in hepatic duct visualization, even in the presence of a normal Vaterian segment. The common bile duct should measure less than 7 mm. in diameter. False-positive dilation of the common bile duct may be produced by failure to recognize those cases in which the cystic and common bile ducts are enclosed in a common sheath and represent two ducts rather than one.

Abnormal radiographic responses to CCK are as follows:

Gallbladder:—There are abnormalities in contraction and emptying. Excessive contraction may involve any portion of the gallbladder. The infundibulum or neck is most commonly involved, however, purportedly because this area of the gallbladder has the greatest investment of musculature.[5] Hypercontraction of the body may produce inefficient emptying of the fundus, just as hypercontraction of the infundibulum or neck results in decreased emptying of the entire gallbladder. Generalized hypercontraction results in emptying of more than 80%. This may occur as early as two to five minutes post-CCK and is manifested by a gallbladder that is string-like in configuration.

Emptying must be distinguished from contraction.

Contraction without emptying is manifested by a change in shape to a more globular form. This is secondary to the gallbladder accommodating its contents to the smaller available geometric space. On the other hand, absence of emptying secondary to absence of contraction is manifested by a lack of change in shape.

Ductal system:—The cystic duct may be narrow, tortuous or severely angulated. The common bile duct may be dilated, measuring more than 7 mm. in diameter. Persistent visualization of the common bile duct, following completion of gallbladder emptying, implies obstruction in the Vaterian segment. The latter may be secondary to spasm or fibrosis. A dilated common duct that empties as the gallbladder empties is of doubtful significance. Such transient dilation may be secondary to prior obstruction.

For purposes of classification, these abnormal responses or findings may be

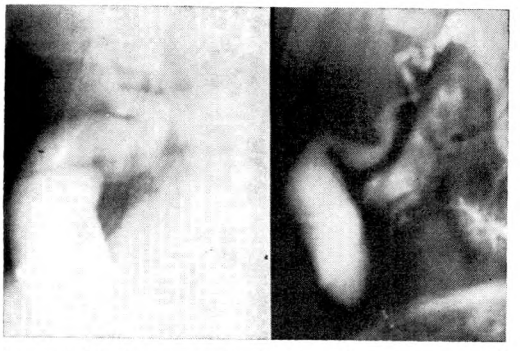


Fig. 5—Tortuous cystic duct. *Left*: Resting gallbladder. Long, tortuous dilated cystic duct. *Right*: Eight minutes post-CCK infusion. Tortuosity of cystic duct more apparent. Dilated CBD with hepatic duct reflux. Free egress into duodenum is evident.

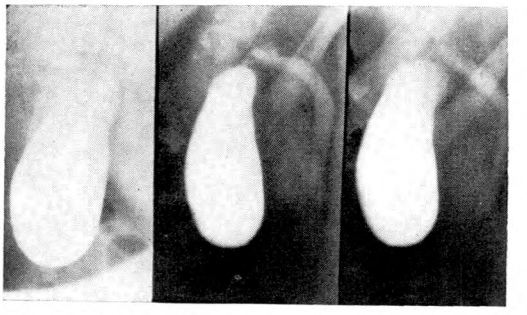


Fig. 6—Fibrosis of the sphincter of Oddi. *Left*: resting gallbladder—faint ductal visualization. *Middle*: Ten minutes post-CCK infusion. The CBD measures 7 mm. in diameter. There is spasm of the gallbladder neck. *Right*: Twenty minutes postinfusion. Relaxation and re-filling are evident, as is persistent opacification of the CBD. Hepatic duct reflux is also present.

listed as follows: 1. Narrowing of the cystic duct, spasm of the neck or infundibulum of the gallbladder (Fig. 2). 2. Spasm of the body or fundus of the gallbladder (Fig. 3). 3. Generalized gallbladder hypercontraction (Fig. 4). 4. Absence of gallbladder contraction. 5. Tortuous or severely angulated cystic duct (Fig. 5). 6. Spasm or fibrosis of the sphincter of Oddi (Fig. 6).

In this study, a positive CCK-GB consisted of both reproduction of the patient's biliary tract-type pain and the appearance of one or more of the aforementioned roentgen abnormalities.

Results

Reproduction of pain:—In 21 of 29 patients, there was reproduction of biliary tract-type pain by the CCK.

Roentgen abnormalities:—In 20 of the same 21 patients with post-CCK reproduction of biliary tract-type pain, roentgen abnormalities were present. With one exception, in the patients without post-CCK reproduction of biliary tract-type pain, no roentgen abnormalities were produced by the CCK. The roentgen abnormalities consisted of: 1. Narrowing of the cystic duct, spasm of the neck, or infundibulum of the gallbladder—11 patients. 2. Spasm of the body or fundus of the gallbladder—three patients. 3. Generalized gallbladder hypercontraction—three patients. 4. Absence of gallbladder contraction—one patient. 5. Tortuous or severely angulated cystic duct—one patient. 6. Spasm or fibrosis of the sphincter of Oddi—two patients.

Positive CCK-GB:—In this study, a positive CCK-GB is defined as both the reproduction of the patient's biliary tract-type pain plus one or more of the aforementioned radiographic abnormalities. Using these criteria, 20 patients had a positive CCK-GB.

Management of CCK-GB positive patients:—Medical management was initially attempted in those patients not already given such a trial. The latter consisted of a low fat diet, antispasmodics, sublingual nitroglycerine and/or long-acting nitrites When medical management failed, as it already had prior to CCK-GB in many patients, cholecystectomy, with or without sphincteroplasty, was carried out. The latter procedure was performed when the CCK-GB demonstrated evidence of obstruction at the sphincter of Oddi. Nineteen

of 29 patients came to surgery. One of these 19 patients had biliary tract-type pain reproduced by CCK, but no roentgen abnormalities. Because, however, of the length and intractable nature of her symptoms, cholecystectomy was carried out.

Histology of removed gallbladder:—In this study, the minimal criteria for chronic cholecystitis consisted of scattered foci of lymphocytic infiltration, the presence of plasma cells in the *lamina propria* and muscle layers and fibrosis. Five of the removed gallbladders showed no histopathologic abnormality. Of the remainder, seven demonstrated chronic cholecystitis, four cholesterolosis and three adenomyomatosis.

Follow-up of patients having surgery:—Follow-up has been carried out through office visits, telephone or letter. Follow-up data were obtained on 18 of the 19 patients subjected to surgery. Seventeen of 18 were cured of their biliary tract-type pain by surgery. In the sole patient with recurrence of right upper quadrant pain, there was a three-year asymptomatic interval between surgery and recurrence of pain. The longest follow-up is now 60 months and the shortest one month.

Comment

In 1946, at the American Roentgen Ray Society's Caldwell lecture, Ivy presented evidence describing the existence of symptomatic biliary dyskinesia involving the sphincter of Oddi.[6] Admitting that this was at that time a difficult diagnosis to establish clinically and roentgenologically, he suggested that the future isolation and use of parenteral CCK might ". . . assist in the solution of the problem." In 1959, following the work of Jorpes, et al[7] intravenous CCK was used not only toward this end, but also to help establish the presence of symptomatic acalculous gallbladder disease and cystic duct disease.

Numerous names have been proposed for these acalculous, extrahepatic biliary tract disorders including the following: 1. dyskinesia, dystonia, and dyssynergia;[8] 2. cystic duct syndrome;[9] 3. hypertonic and hypotonic dyskinesia;[10] 4. hypercontraction of the gallbladder;[11] 5. focal spasm of the gallbladder[5] and 6. stenosis of the sphincter of Oddi.[5]

Regardless of the label applied, all of these entities are characterized clinically by episodic biliary colic and a normally visualizing, acalculous oral cholecystogram. Administration of CCK to such patients usually resulted in reproduction of biliary tract-type pain and/or radiographic changes permitting classification into one of the above categories. Initial management of such patients is usually medical and then, when this fails, cholecystectomy with or without sphincteroplasty. Histologically, removed gallbladders revealed either no abnormalities or changes consistent with cholecystitis, cholesterolosis, or adenomyomatosis. Postoperatively, 91-100% have been reported to be cured.[5, 10-14]

This paper documents an experience with CCK-GB in 29 patients. In contradistinction to some of the other studies, a positive CCK-GB in this group necessitated both post-CCK duplication of the patient's biliary tract-type pain and one or more of several post-CCK roentgen abnormalities. Our management—initially medical and then surgical—is similar to that described by other authors as was the spectrum of histologic changes in removed gallbladders. The cure rate of 95% in this series is similar to that reported elsewhere.[5, 10-14]

The sole dissenting opinion concerning CCK-GB comes from Dunn, et al[15] who state ". . . cholecystokinin cholecystography, as currently performed, is of little or no value in the diagnosis and management of patients with possible acalculous

biliary tract disease." Their reasons were: 1. the incidence of post-CCK abnormal contractions in their control subjects was high; 2. both CCK-positive and CCK-negative patients with symptomatic acalculous gallbladder disease were cured by cholecystectomy; 3. CCK-positive and CCK-negative gallbladders removed at surgery from the above patients had similar histologic findings and 4. in approximately 28% of cases, one of the three radiologists differed in a major way from the other two in interpretation of the roentgenograms.

Goldstein, et al[11] believe that the high incidence of post-CCK abnormal contractions in Dunn's control group may be attributed to the 45-second injection period utilized in their study. Torsoli, et al[16] demonstrated that a 30-second injection of CCK produced spasm of the gallbladder neck without significant gallbladder emptying. Goldstein, et al[11] and others,[13, 14] including ourselves, use a slow three-minute injection and, under these circumstances, abnormal contractions are not seen in controls. It would be interesting to know in how many of Dunn's controls the abnormal radiographic response was indeed spasm of the gallbladder neck.

In Dunn's series[15] 29 patients were subjected to cholecystectomy and, of these, nine did not have their symptoms reproduced by CCK. Of these nine, six were improved or cured by cholecystectomy. From Dunn's data, it is difficult to ascertain whether or not these six patients included the two in their series who had unsuspected cholelithiasis at surgery. One of our patients, with a negative CCK-GB study, was also found to have unexpected cholelithiasis at surgery. Another possible explanation for Dunn's six patients was that their gallbladders contained cholesterol crystals. The latter, when obtained by duodenal drainage, implies either cholelithiasis or cholesterolosis of the gallbladder.[17] In the Freeman, et al study[10] dealing with CCK-GB (called cholecystokinin cholangiography by their group), there were four patients with cholesterol crystals obtained by duodenal drainage who had neither pain nor delayed emptying of the gallbladder after a CCK injection. All were cured by cholecystectomy. It is thus evident that not all symptomatic acalculous gallbladder disease will have a positive response to CCK.

In all reported series,[5, 10-15] removed gallbladders have demonstrated either no abnormalities or findings consistent with chronic cholecystitis, cholesterolosis or adenomyomatosis. No one has claimed that CCK-GB has the ability to predict histologic findings in a gallbladder. Rather, CCK-GB is attempting only to reproduce symptoms in a target organ, regardless of what the etiology of the symptoms might be. These etiologies include neuromuscular dysfunction, hence probably the normal gallbladders, as well as the histopathologic entities listed above.

We are unable to explain the high degree of observer disagreement in the Dunn series.[15] This has not been a problem in other series nor in our hands.

In view of the results in all reported series,[5, 10-14] including our own, and in disagreement with Dunn, et al,[15] we conclude that CCK-GB provides a reliable study for the diagnosis of acalculous extrahepatic biliary tract disorders.

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Communication from Abroad

The Clinical Course of Subacute Hepatic Necrosis

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The clinical course is reported in 17 patients in whom the histological picture of subacute hepatic necrosis ("bridging hepatitis") was found on needle liver biopsy or at autopsy.

The patients' ages ranged from 10-71 years, 12 patients being less than 40 years old. Ten patients were males. Jaundice lasted 2-4 months in nine cases and over six months in two, one of the latter having developed cirrhosis.

In five patients a relapse of jaundice occurred within three months. Hepatitis B antigen was found in one of 13 patients tested. Two patients died in fulminant hepatic failure, one developed cirrhosis. These three patients and an additional two received prednisone therapy.

Twelve of the remaining patients were followed for periods of 8-81 months; an additional two patients' follow-up was incomplete. None developed clinical evidence of chronic liver disease, and laboratory data at the last examination were normal except for slight elevation of alkaline phosphatase in six cases. Repeat biopsies showed persistent hepatitis in one case, slight portal fibrosis in one, cirrhosis in one and at autopsy in a patient who died of unrelated causes two years after hepatitis no evidence of chronic liver disease was found.

This relatively good outcome of subacute hepatic necrosis is probably due to the young average age of the patients, and the low incidence of B hepatitis in this series.

Subacute hepatic necrosis, (SHN) characterized by areas of necrosis forming bridges between portal triads or between portal triads and central veins, was described by Boyer and Klatskin[1] as a severe form of viral hepatitis with considerable immediate mortality and frequent transition into cirrhosis. Subsequently this histological picture was described as part of the spectrum of chronic active hepatitis.[2-5]

In contrast to earlier reports associating SHN with a poor prognosis, later reports showed that the outlook was not quite as grim.[2,3,5,6] We here report a series of 17 patients in whom the histological picture of SHN was found on needle liver biopsy or at autopsy.

Material and Methods

Patients:—At our hospital needle liver biopsy is performed in patients with viral hepatitis only if the case is more severe or

From the Gastroenterology Unit, Tel Hashomer Hospital.

TABLE I

GENERAL DATA

Sex	
Male	10
Female	7
Age	
Under 40 years	12
Over 40 years	5
Soldier	7
Epidemiology	
Contact with hepatitis	1
Previous blood transfusion	4
Injections	2
Medication	
Methyl dopa	1 (Case 9)
Chlorpropamide	1 (Case 16)
Additional diseases	
Hodgkin's disease	1 (Case 14)
Alcoholism	1 (Case 15)

TABLE II

CLINICAL DATA

Anicteric course	2
Duration of symptoms prior to onset of jaundice	
Up to 1 week	14
1-2 weeks	1
Liver size, below ribs	
Not palpable	3
2-4 cm.	10
5-10 cm.	4
Spleen size, below ribs	
Not palpable	10
1-3 cm.	4
4-6 cm.	3
Coma	2
Relapsing course	5
Interval between separate episodes of hepatitis	
Up to 1 month	2
1-3 months	3

protracted than usual. Patients were entered in this series solely on the basis of a histological finding of SHN, discovered on needle liver biopsy (15 patients) or at autopsy (2 patients).

The patients were admitted to the medical or pediatric service during the years 1968-1973.

Laboratory investigation:—Serum bilirubin, SGOT, proteins, alkaline phosphatase, iron and prothrombin time were determined by standard methods. HB antigen was tested for by immunodiffusion. In three patients sera were tested for HB-Ag and HB-Ab by radioimmunoassay several years following their acute illness.

Liver biopsy:—This was obtained with the standard Menghini needle, using the intercostal approach. Biopsies were fixed in Carnoy's solution, cut at 6 micron serial sections and stained with hematoxylin-eosin and Masson's trichrome connective tissue stain. The histological interpretation was performed by one of the authors (E.T.)

RESULTS

General data (Table I):—The patient's ages ranged from 10-71 years, 12 being under 40 years old. There were 10 males and seven females. Seven of the patients were serving in the Israel Defense Army when they contracted hepatitis. Only one patient had been in contact with cases of jaundice. Two had received injections by the family physician, four had received blood transfusions and two patients had been treated with medication known to cause liver damage—chlorpropamide in one case and methyl dopa in the second. The latter patient, however, resumed taking this medication, due to an oversight, without evidence of recurrent liver damage.

Additional diseases:—Case 14 had Hodgkin's disease, treated with radiation. Case 15 was an alcoholic who reduced his alcohol intake drastically since he had hepatitis.

TABLE III

LABORATORY DATA

Peak bilirubin, mg./dl.		
1-10	7	
11-20	4	
21-30	5	
Over 30	1	
Time taken to reach peak bilirubin		
1-2 weeks	8	
3-4 weeks	5	
Over 4 weeks	4	
Duration of bilirubinemia		
Under 2 weeks	3	(2 fatal)
1 month	3	
2-4 months	9	
Over 6 months	2	
Peak SGOT		
200-500 U.	6	
500-1,000 U.	8	
Over 1,000 U.	3	
Minimal prothrombin time (%)		
Under 30	2	
30-50	7	
50-70	8	
Minimal albumin, gm./dl.		
1-2	2	
2-3	5	
Over 3	10	
Maximal globulin, gm./dl.		
2-4	8	
4-5	6	
Over 5	3	
Peak alkaline phosphatase, I.U.		
45-100	8	
100-200	5	
200-400	4	

Clinical findings (Table II):—Two patients had an anicteric course. In almost all the other patients the prodromal symptoms lasted one week or less before jaundice appeared.

Most patients suffered, in varying combinations, from anorexia, nausea, vomiting, abdominal pain, fever and pruritus. In six patients weight loss up to 5 kg. was noted prior to admission.

Liver size:—The liver was usually moderately enlarged. In the two patients who died of acute liver failure the liver was not palpable, and on percussion was decreased in size (4cm., 7cm.). In one other patient (Case 15) the liver was not palpated during the hepatitis.

Spleen size:—The spleen was not felt in 10 patients (Case 14 was postsplenectomy) and was moderately enlarged in the others.

Coma:—Two patients developed fulminant hepatic failure with coma. Both died, after coma lasting eight and nine days, respectively.

Relapsing course:—In five patients jaundice subsided and liver function improved markedly but after intervals of three weeks to three months they had a recurrent episode of hepatitis. The second bout was more prolonged and abnormalities of liver function more pronounced in two patients —Case 17 and Case 12 who progressed to cirrhosis. In the other three (Cases 2, 5, 9) the recurrence was similar to the first bout of hepatitis.

Laboratory findings (Table III):—The peak bilirubin reached by each patient varied from 1.1 to 38 mg./dl. and was over 20 mg./dl. in six patients. The time taken for bilirubin to reach its peak varied from three days to 22 months (in the patient who developed cirrhosis). Total duration of jaundice in over half the cases was between two and four months. SGOT levels were high in most patients, in the range expected in hepatitis. Prothrombin time decreased variably but was below 30% (11%, 12%) only in the fatal cases and in seven patients ranged between 30%-50%. Serum albumin levels decreased moderately in five patients and markedly (below 2 gm./dl.) in two patients, both of whom recovered from their liver disease. Serum globulin rose

TABLE IV

OUTCOME OF SHN AT LAST VISIT

Case	Death	Length of follow-up (mo.)	Liver Cm.	Spleen Cm.	Bilirubin TOT/DIR	SGOT	Alkaline phosphatase	Albumin globulin	Prothrombin	Repeat biopsy	Prednisone
1		5	TIP	TIP	Not performed at last visit						+
2		52	1.5	0	0.6	12	17	4.2/2.4	75%		
3		32	1.5	2	0.4	16	26	4.7/2.3	80%	Persistent hepatitis	
4		8	2	0	0.4	30	*54*	4.5/2.5	80%		
5		45	1.5	0	0.4	20	40	5 /2.3	100%		
6		37	TIP	0	0.4	40	*50*	4.1/2.6	75%		
7		19	2	0	0.4	36	*59*	4.5/1.7	90%		
8		31	1	2	0.4	24	*58*	4.4/2.7	70%	Sl. Portal fibrosis	
9		36	5	0	0.4	12	*50*	4.3/2.8	75%		
10	+										
11	+ (unrelated)	27	10	0		*80*		2.0/2.7		Normal liver (PM)	+
12		30	3	TIP	4/3.2	*71*	*212*	4.8/2.7		Cirrhosis	+
13	+										+
14		81	3	Oper	0.7	18	*60*	5.1/3.0			+
15		52	3	0	0.7	36	47	4.0/2.5	90%		
16		8	4	0	0.8	*57*					
17		36	TIP	0	0.4		27	4.3/3.3	80%		

Numbers in italics represent abnormal values (upper limit of alkaline phosphatase was 45 units).

moderately in most patients, but not over 5 gm./dl. in 14 of the cases.

Alkaline phosphatase was elevated in 13 cases not higher than 5 times normal. Most hepatitis B antigen determinations were done by immunodiffusion. Of 13 determinations performed during the disease, only one was positive. Antibodies to hepatitis B were looked for in eight patients at the time of illness and none were found.

In three patients hepatitis B antigen and antibodies were looked for three years (Cases 6, 9) and four and a half years (Case 15) following the acute illness. The only positive test was hepatitis B antibodies in Case 15.

Antinuclear factor was looked for in five patients and was positive in one case (Case 9). No tests for smooth-muscle and mitochondrial antibodies were done.

Clinical course (Table IV):—Two patients (Cases 10 and 13) died in acute liver failure. One patient developed cirrhosis in serial liver biopsies (Case 12). She suffers from pruritus and laboratory tests relating to the liver are continually abnormal. The other patients were followed for periods of two to 81 months, 10 of them over 19 months.

One patient (Case 11) died 26 months after the onset of hepatitis, the cause of death being pneumonia complicated by massive pulmonary embolism. The liver at autopsy showed a normal architecture, infiltration by lymphocytes and hematopoietic cells, some congestion and fatty change but no fibrosis or parenchymal necrosis. The follow-up is incomplete in one patient (Case 1). In 12 patients followed for eight to 81 months, complete or almost complete recovery ensued. None of the patients complained of anorexia, weight loss, swelling of the abdomen or legs, jaundice or pruritus. The liver size at the last visit ranged from not palpable to 5 cm. The spleen was palpable in three patients. None of these 12 patients had physical signs of chronic liver disease. Laboratory tests were normal except for slightly elevated alkaline phosphatase in six patients.

Follow-up biopsies were performed in three patients. They showed cirrhosis in Case 12, persistent hepatitis in Case 3 and slight portal fibrosis in Case 8.

Prednisone therapy:—This was given in five patients. In Case 1 follow-up is incomplete. In Cases 10 and 13 prednisone was given as part of the management of fulminant hepatic failure and both died. In Case 12 cirrhosis developed under intensive prednisone therapy. Case 14 received prednisone for three months without effect on bilirubin and SGOT but subsequently recovered.

It is clearly impossible to assess the effects of prednisone therapy in our series from these limited data.

Comment

The clinical course in our patients was on the average more severe than that of ordinary hepatitis—bilirubinemia was more severe and lasted longer than expected in viral hepatitis and two cases developed coma. This parallels the experience of Boyer and Klatskin,[1] while in the series of Ware, Eigenbrodt and Combes[5] quite a few cases of SHN had clinically mild disease. Five of our patients (29%) had a relapsing course, also in keeping with the experience of Boyer and Klatskin, where a relapsing course was seen more commonly in SHN (23%) than in classical hepatitis (11%).

Causative agent:—In our series, only one case out of 13 tested had hepatitis B antigen demonstrated during active disease

and an additional patient had hepatitis B antibodies four and a half years following hepatitis. With the reservation that the method used was immunodiffusion, which is the least sensitive method for detecting HB-Ag, it is likely that most patients did not suffer from B hepatitis. This impression is reinforced by the fact that seven patients were soldiers, who are much more likely to contract epidemic (A) hepatitis. The incidence of HB-Ag positivity in published series of SHN is high[3,5,7] and in the series of Boyer and Klatskin, serum hepatitis (diagnosed on epidemiological grounds) was more frequently associated with SHN than was epidemic hepatitis. Furthermore, none of the cases of SHN associated with epidemic hepatitis died or developed cirrhosis. If indeed the causative agent determines how serious the outcome of SHN is, then quite probably the generally good outlook regarding full recovery in our patients may be related to the high incidence of HB-Ag negativity (and thus probably hepatitis A) in our series.

Age:—Our patients were mostly under 40 years of age. While the two cases of fatal hepatitis were among this young age group, the over all eventual good outcome may be related to the age factor. In the series of Boyer and Klatskin, 63% of the patients were over 40 years old. Peters[6] feels that this may be a major factor in determining the outcome of SHN, in that younger patients are capable of regenerating damaged liver tissue, while patients over the age of 40 cannot and succumb.

Outcome of SHN:—In our series two patients died in fulminant hepatic failure and one developed cirrhosis. Of the remaining 14, adequate follow-up data are available in 12; in three histological and in the others clinical only. None of the patients developed evidence of chronic liver disease or cirrhosis.

The paucity of follow-up biopsies in our series is unfortunate, since in other series a variable proportion of asymptomatic patients had cirrhosis on repeat biopsies[1,5] and this might be the case in some of our patients. With this reservation, the outcome of SHN in the present series was good in a high proportion of patients, compared to the grim outlook in the early series.[1] This relatively good outcome becomes even more significant since liver biopsy was performed only in more severe or protracted cases of hepatitis, as noted in the "materials and methods" section. Our findings of a more hopeful outlook in SHN is in keeping with the experience of several other series.[2, 3, 5, 8] The incidence of cirrhosis in the present series was low—1/17 or 6%. In other series the incidence was none,[3] 9%[5] and 37%.[1] Of interest is the finding by Karvoutzis, Redeker and Peters.[8] The histological picture of SHN was seen in one half of 22 patients biopsied during recovery from fulminant hepatitis. None of them developed cirrhosis. The mortality in our series was 2/17 or 12%. In other published series the mortality of SHN ranged from 2% to 19%, the average being 10%[1, 3, 5, 7]

Response to therapy:—While two recent series published as abstracts claim good results for therapy with prednisone and Imuran,[3, 4] no effect of therapy could be shown in three other series.[1, 2, 5] In our series, prednisone was given to two patients in coma without effect, one patient developed cirrhosis under therapy and of the patients who did well, two received treatment (one lost to follow-up) and 12 did not (one with incomplete follow-up). Clearly prednisone therapy had no effect in our patients.

In our cases there were no associated systemic manifestations suggestive of "autoimmune" chronic active hepatitis such as arthritis, colitis, etc. Antinuclear factor was

looked for in five patients and was positive in one, who received no prednisone and was clinically well three years later (Case 9). It would seem that our cases of SHN were due to hepatitis, without an autoimmune component but immunologic data to confirm this (such as smooth-muscle antibodies) are lacking.

Future studies on the effect of corticosteroids in SHN will have to separate cases due to acute viral hepatitis from those constituting part of the spectrum of chronic active hepatitis, and among the latter—differentiate between cases with "autoimmune" features as opposed to those lacking these features but being HB-Ag positive.

The importance of separating the cases according to etiology is emphasized because a recent report[9] seems to indicate that steroids may actually be detrimental in SHN due to acute viral hepatitis.

Conclusion

In the series of SHN here reported, the mortality was comparable to other published series, the incidence of cirrhosis relatively low and no patient developed clinical or laboratory evidence or chronic liver disease, although most patients did not receive prednsione.

The young age of our patients and the high incidence of HB-Ag negative, probably hepatitis A, are likely explanations for this relatively good outcome of SHN.

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Communication from Abroad

An Epidemic of Veno-occlusive Disease of the Liver in Afghanistan

Pathologic Features

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A large outbreak of veno-occlusive disease occurred in Afghanistan in which approximately 7,800 in a population of 35,000 subjects were estimated to have been affected. It was caused by consumption of wheat flour heavily contaminated with seeds of a plant of the heliotropium species. These were found to contain pyrrolizidine alkaloids, chiefly heliotrine. Fourteen percutaneous liver biopsies, representing different stages of diseases and liver tissue from eight autopsies were studied. Morphological changes in the liver were characteristic. Centrilobular hemorrhagic necrosis was followed by occlusive changes in the hepatic veins, finally resulting in nonportal cirrhosis. The sequence of changes observed suggests primary parenchymal injury and possibly obstructive lesions at the sinusoidal level. Collagenization of the sinusoids and reorganization of the lobular reticulin begin early in disease. Occlusive changes in the efferent veins apparently follow.

Veno-occlusive disease was first described in man by Bras, et al[1] as an endemic disease in the West Indies. It was believed to be an important cause of cirrhosis in that region.[2] The disease was attributed to drinking concoctions made from indigenous plants containing a pyrrolizidine group of alkaloids. There are earlier accounts of the toxic effects of these alkaloids in animals and man[3] and several reports of sporadic cases from different parts of the world.[3-9] Until recently, however, only a few outbreaks of acute intoxication have been described.[10-13] We have had an unusual opportunity to study two such outbreaks in India[14-16] and one in Afghanistan,[17] during the last three years. The latter is the largest outbreak on record and has been partly reported.[18] We report here the detailed pathologic features of this unusual disease, as observed in this outbreak.

The Epidemic

The epidemiological and clinical features of this outbreak were reported earlier.[18] Briefly stated, a large scale epidemic occurred in the Herat Province of Northwest Afghanistan that affected a population

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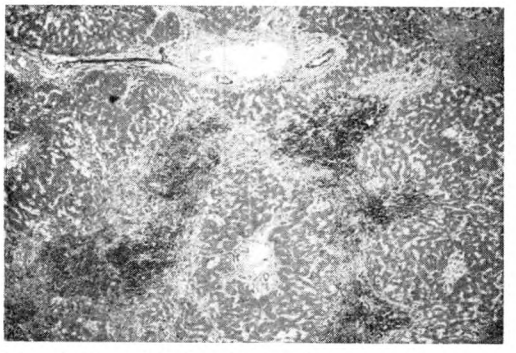


Fig. 1—Centrilobular hemorrhages and necrosis (Hematoxylin and eosin, original magnification x28).

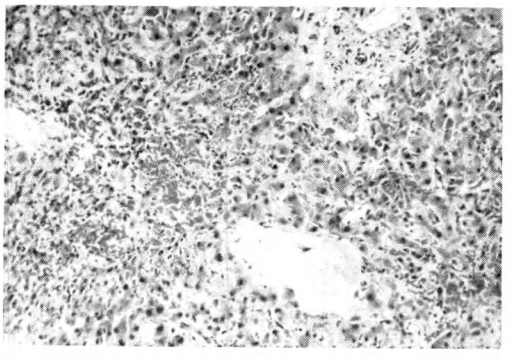


Fig. 2—Dilated and widely patent central vein. The paracentral sinusoids are distended with blood (Hematoxylin and eosin, original magnification x96).

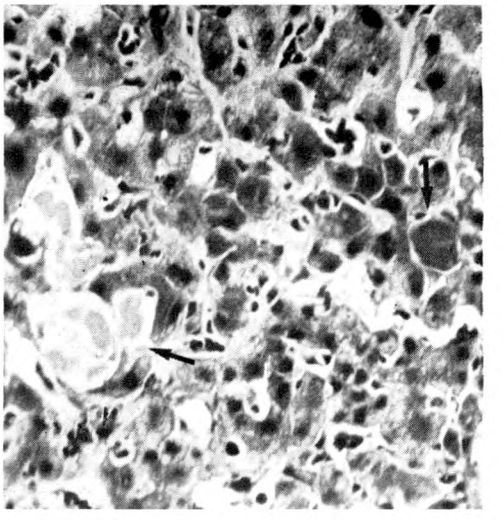


Fig. 3—Precipitates of fibrin-like material plugging the sinusoids (arrows). (Hematoxylin and eosin, original magnification x200).

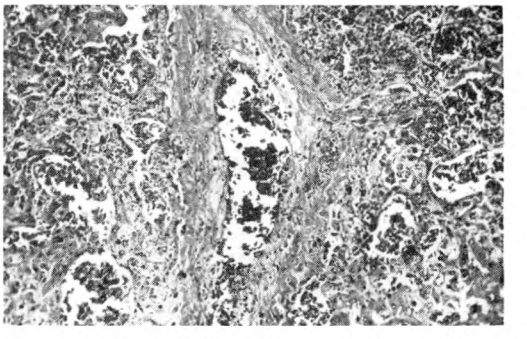


Fig. 4—Severely thickened central vein. There is prominent subendothelial edema with hemorrhages. The pericentral sinusoids are dilated. (Hematoxylin eosin, original magnification x96).

of about 35,000 people in 98 villages. Examination of the inhabitants showed evidence of liver disease in 22.6%.[18] Dragging pain in the right hypochondrium and rapidly developing ascites were characteristic features but jaundice was uncommon. The disease was ascribed to the consumption of bread made of wheat flour, that was heavily contaminated with the seeds of a plant of the heliotropium species. The plant was found overgrowing the wheat crop, as reported earlier.[17, 18] The clue was provided by a villager who had fed his flock of sheep with this plant about two years previously. On slaughter, the livers were found to be shrunken and granular and ascites was present. All age groups were affected. Several members of a family became ill at the same time or within a short interval. The disease was often fatal.

The contaminating seeds were confirmed to have the pyrrolizidine group of alkaloids in toxic quantities, notably heliotrine and its nitrous oxide. Among the several other alkaloids present, at least one had the chemical features of a heliotridine diester which was similar to but not identical with lasiocarpine.

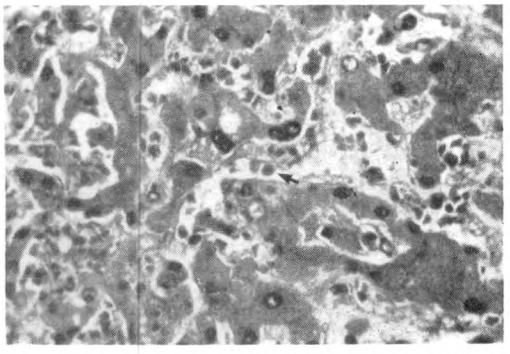


Fig. 5—Extravasated red blood cells in dilated space of Dissé (arrow) (Hematoxylin and eosin, original magnification x320).

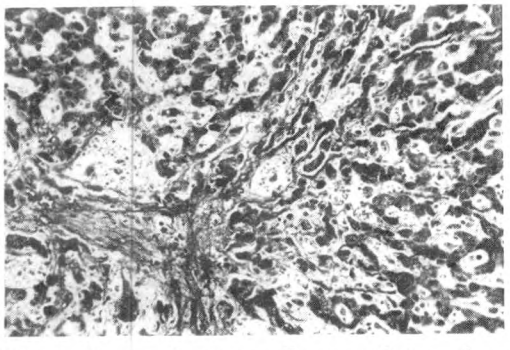


Fig. 6—Bands of wavy collagen radiating from thickened central veins and running along the sinusoids (Hematoxylin and eosin, original magnification x96).

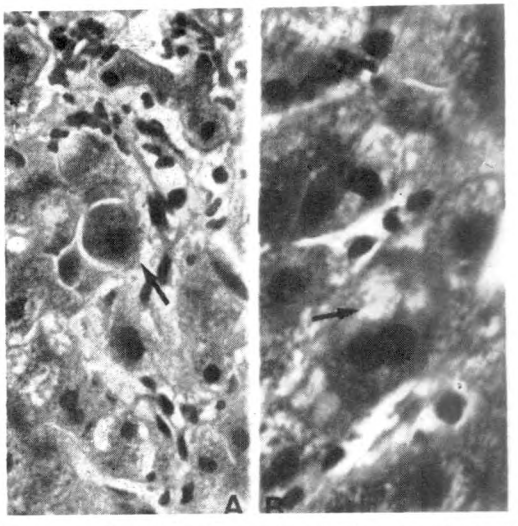


Fig. 7A—Partial hyalinization of the cytoplasm of a hepatocyte, which is shrunken away from the cytoplasmic boundaries (arrow) (Hematoxylin and eosin, original magnification x320).

Fig. 7B—Hepatocyte containing a sheaf of linear vacuoles (arrow) (Hematoxylin and eosin, original magnification x400).

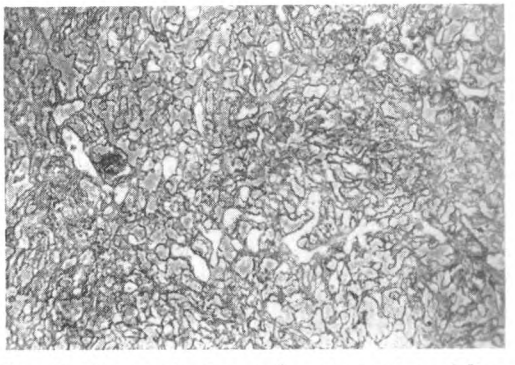


Fig. 8—Disorganization and sequestration of liver cell plates (Reticulin, original magnification x96).

Material and Methods

Material studied consisted of 14 liver biopsies, performed during the field visits. In addition, liver tissue was available from eight autopsies. The tissues were fixed in neutral buffered formalin and processed for section cutting in paraffin. Tissue sections were stained with hematoxylin and eosin and for reticulin, elastic tissue and connective tissue. Material was also taken for ultrastructural studies (to be reported separately).

Pathologic Changes

The most conspicuous change was severe centrilobular sinusoidal congestion and hemorrhagic necrosis (Fig. 1). Occasionally, lagoons of extravasated blood were seen infiltrating the centrizonal scars or around thickened veins. The hepatic veins constituted the pivotal point of pathologic change. Very often they could not be identified or appeared only as wavy bands of collagen in zones of hemorrhage.

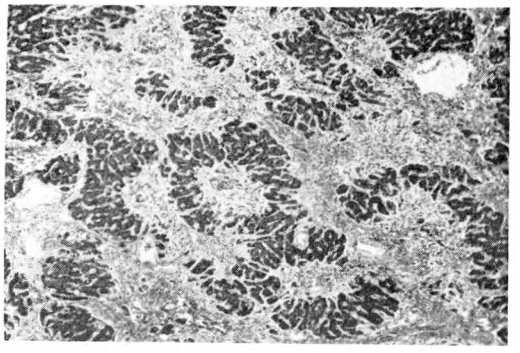


Fig. 9—Nonportal cirrhosis (Masson Trichrome, original magnification x28).

It was not unusual for the central veins to be markedly dilated but empty and surrounded by congested sinusoids (Fig. 2) or acellular zones of edematous collagen. In one such case, the sinusoids in the mid zone of the lobule were choked with a bright red granular acellular material resembling a fibrin plug (Fig. 3). Some veins were severly thickened and fibrosed, yet widely patent. Classically, there was a varying degree of occlusion which occasionally was almost total. The thickening was contributed to by subintimal edema, hemorrhage or collagen (Fig. 4). No thromboses were seen. There was compensatory dilatation of pericentral sinusoids. In one case, the space of Dissé was dilated and filled with exudate and extravasated erythrocytes (Fig. 5); the latter were also seen ingested by the Kupffer cells.

A conspicuous feature was the collagenization of sinusoids which was seen quite early in the disease. Bands of thick wavy collagen were seen to radiate from the sclerotic veins (Fig. 6). In due course, the liver cell plates became broken up into small islets. The collagenous tissue was infiltrated by a variety of chronic inflammatory cells; polymorphonuclears were prominent in the early stages but inflammatory or Kupffer cell reaction was never particularly severe.

The hepatocytes showed a variety of necrotic or degenerative changes in all stages of the disease. These were particularly severe in the early and acute cases. They were most marked in the pericentral zone, around hemorrhagic areas. Sometimes they were seen as irregular, attenuated branching columns surrounded by an-acute inflammatory infiltrate. Their cytoplasm was partly hyalinized and shrunken away from the cell boundaries (Fig. 7A). In one case, occasional cells contained what resembled a sheaf of linear vacuoles (Fig. 7B) in the cytoplasm. Some cells contained globular hyaline. Often, the cells were distended, their outlines hazy and their cytoplasmic contents coarsely fragmented. Nuclei showed varying degrees of pynknosis, karyolysis and vacuolation. There was no cholestasis and fat was an inconspicuous feature. Cellular regeneration was never dominant. There was no megalocytosis.

The lobular reticulin was sometimes completely destroyed in the centrilobular necrosis but generally was collapsed and reduplicated in this area. In many cases the hepatocyte plates were disorganized and sequestered into small islands circumscribed by thick reticulin, even in the acute phases of the disease (Fig. 8).

The portal tracts were generally enlarged and sclerotic. In the later stages, they tended to link with each other or with the central veins. In advanced disease, a micronodular nonportal cirrhosis, starting primarily in the efferent vein territory, was seen in five cases (Fig. 9). Sometimes, the pseudolobules were very small, comprising only a few cells each. Regenerative nodules were uncommon. No bile duct prolifieration was seen. In one biopsy the fibrosis was pericellular.

Comment

The morphological features as observed in our patients are classical of the

disease.[1, 19-23] The etiology is suggested by the epidemiologic and clinical observations. The wheat crop was overgrown with a plant of heliotropium and the grain stores in affected households were found heavily contaminated by their seeds. Families who had cleaned their wheat were not affected, whereas several members in a family who did not do so were affected. The seeds have been found to have toxic concentrations of pyrrolizidine alkaloids most notably heliotrine, in addition to several others chemically similar to lasiocarpine.

Apart from Jamaica where the disease is stated to be endemic, there are numerous reports of sporadic cases from several parts of the world.[3-9, 21] Previously reported outbreaks have been much smaller. Those described by Willmot and Robertson[11] and Selzer and Parker.[10] from South Africa affected only 11 and 12 cases, respectively. In both these outbreaks, the causative agent was the seeds of plants of the senecio species. Both these studies emphasize the vulnerability of subjects of poor socioeconomic status. This would be applicable to our cases as well. Their nutritional status was poor. Since wheat bread is their staple diet, consumption of the toxic material was large.[18] Outbreaks reported by Savvina[12] and Braginski and Bobokhadzaev[13] were caused by contamination of food by seeds of heliotrope, as in our cases. The 61 subjects reported by Braginski and Bobokhadzaev were affected; they developed ascites 10-12 months after poisoning and none died. In the epidemic herein reported, approximately 7,800 subjects were estimated to have been affected and mortality was approximately 25%.

McLean[25] has given an exhaustive account of the toxic actions of the pyrrolizidine alkaloids. There are over 240 species of plants known to contain such alkaloids. Bull, Culvenor and Dick[26] include in their list 12 heliotropium, 102 senecio and 44 crotalaria and there are other plants not yet investigated. Over 100 pyrrolizidine alkaloids are known, but not all of these are hepatotoxic. Most human cases are known to be caused by lasiocarpine. Heliotrine is believed to be uncommon but the outbreak studied by us was caused chiefly by heliotrine. Veno-occlusive changes due to this alkaloid have been less frequently reported than the veno-occlusive changes which follow consumption of seeds of the crotalaria species. The two outbreaks that we have reported from India[14-16] were found to have been caused by crotalaria.

Since studying the above outbreaks, we have had two sporadic cases who were seen in the acute phase of the disease. In at least one, the disease was traced to the use of some indigenous herbs, which may have contained such alkaloids.

Pathology and Pathogenesis

Certain features observed by us are of interest in regard to pathogenesis. It was not unusual to see widely patent and, indeed, dilated central veins surrounded by a zone of dilated sinusoids or hemorrhagic necrosis (Fig. 2). In one such case, a group of sinusoids was choked with plugs of a hyalin or granular material, possibly fibrin (Fig. 3). Extravasation of blood was observed in the space of Dissé (Fig. 5) and between hepatocytes. Evidence of diffuse parenchymal disease was present in practically every case. Reticulin framework was either destroyed, though rarely in the centrilobular zones, or collapsed. More interesting is the observation that fairly early in the disease, when the central zones of the lobules were still pools of blood, the reticulin framework had been reinforced in the peripheral zones of the lobules and the liver cell plates sequestered into small circumscribed islets (Fig. 8). Even in the

early stages, thick bands of wavy collagen were seen creeping out along the sinusoids radiating from the central zones.

Earlier accounts[1, 20] emphasize the veno-occlusive changes as the initial event and hemorrhagic necrosis and parenchymal damage as later developments. Our observations indicate a primary lethal effect on the parenchyma and confirm more recent studies.[3, 9, 25, 27] "Serous exudation" in the sinusoids was first described by Hill, et al[28] but fibrin and extravasted red cells in the space of Dissé have been demonstrated by Brooks, et al[22] in ultrastructural studies and by Leopold, et al[29] in light microscopic studies. In addition, there is now a great deal of experimental evidence indicating that blockage to the vascular flow occurs primarily in the sinusoids following primary injury to the hepatocytes and sinusoidal epithelium.[22, 23, 30-33] We did not observe deposition of fibrin at the entrance of the sinusoids into the central vein but plugs of fibrin-like material were observed occupying the sinusoids in the mid zone in one case. In addition, the presence of exudates and extravasated blood in the sinusoids, collagen extending to the sinusoids and proliferation of reticulin disorganizing the liver cell plates may all explain the "early outflow block"[25] and the appearance of symptoms and signs of portal obstruction noted early in the disease.

It is to be emphasized that megalocytosis was not present. Bull and Dick[34] have described this characteristically in the livers of sheep that had grazed on heliotropium for two seasons. This is known to be present in a number of species of animals given multiple doses of alkaloids. There is no mention of this change in humans including those of Braginski and Bobokhadzaev[13] in their four-year follow-up study. It is possible that human liver cells react differently.

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Sclerosing Cholangitis Associated with Ulcerative Colitis

Light and Electron Microscopy Studies

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The light and electron microscopy findings of liver biopsies from four patients with sclerosing cholangitis and ulcerative colitis are described. The main histologic feature was mesenchymal proliferation involving phagocytic, fibroblastic and immunocytic cells suggestive of an immunologic type of liver injury which may attack bile duct epithelial cells. Other histologic features, included the presence of myelin fibers in both hepatocytes and bile duct epithelial cells and an abundant amount of lysosome-like structures. The significance of these findings is discussed.

Introduction

Primary sclerosing cholangitis is a rare disorder characterized by progressive fibrous thickening and stenosis of both intrahepatic and extrahepatic bile ducts.[1-3] Since Delbet's original presentation in 1924[4] many cases have been reported and by 1973 there were 100 acceptable cases in the world literature.[5] Primary sclerosing cholangitis occurs more frequently in association with ulcerative colitis than with any other disease[6-8] although its incidence is less than 1% among patients with ulcerative colitis.[9] Recently the findings of endoscopic retrograde cholangiopancreatography (ERCP) were reported in two patients with ulcerative colitis and sclerosing cholangitis.[10] This paper reports the results of light and electron microscopy studies of liver biopsies obtained from four patients with sclerosing cholangitis associated with ulcerative colitis.

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Materials and Methods

The criteria set forth by Cutler and Donaldson[11] were considered essential for inclusion of patients in this study. These include: 1. absence of previous surgery; 2. absence of gallstones; 3. generalized narrowing of either intrahepatic or extrahepatic ducts or both; 4. absence of primary biliary cirrhosis and 5. absence of malignancy. All patients had ulcerative colitis several years before pathological changes were identified in the liver.

Liver biopsies were performed percutaneously by either a Menghini needle or a disposable needle (Travenol). Approximately three quarters of the specimen was processed for paraffin embedding. Sections were stained by hematoxylin and eosin, periodic acid-Schiff reagent (PAS), trichrome for collagen and fibrin and Perl's Prussian blue for iron and examined by light microscopy. For electron microscopy, cubes of liver tissue approximately 1 cu. mm. were fixed in 2% cold glutaraldehyde for three hours. The specimens were transferred to a cold solution of sodium cac-

TABLE I

CLINICAL DATA

Patient	Age	Sex	Duration of colitis at onset of sclerosing cholangitis	Activity of colitis	Jaundice	Hepatomegaly	Splenomegaly	Portal hypertension with varices	Itching	Bone disease
Case 1 (FF)	44	M	3 years	Colectomy	+	+	+	+	+	+
Case 2 (RT)	22	M	3 years	Inactive	+	+	−	+	+	+
Case 3 (LO)	70	M	30 years	Mild	−	+	+	+	+	+
Case 4 (WS)	32	F	3 years	Mild	+	+	+	+	+	+

Fig. 1—Liver biopsy showing marked portal fibrosis and focal destruction of the limiting plate. There is marked infiltration by "chronic" inflammatory cells (Hematoxylin and eosin, original magnification x100).

odylate containing 3% sucrose at pH 7.4 and postfixed in osmium tetroxide for two hours. They were then dehydrated with increasing concentrations of ethanol and embedded in Epon. Thin sections (600 A to 800 A) of three to four blocks from different lobular zones were stained with uranyl acetate and citrate, followed by examination with an RCA EMU-3G electron microscope.

RESULTS

The clinical and laboratory data of the patients are summarized in Tables I and II.

The morphological changes observed in liver biopsies are represented mainly by portal fibrosis associated with bile duct proliferation. The limiting plate shows focal destruction with infiltration of inflam-

TABLE II

LABORATORY DATA

Patient	SGOT I.U.	Alkaline phosphatase I.U.	Serum bile acids μMol/l.	Bilirubin mg./dl.	Serum albumin gm./dl.	Ig-M mg./dl.	Ig-A mg./dl.	Ig-G mg./dl.	Prothrombin activity (%)	HBsAg	Ca^{++} mg./dl.	P mg./dl.
Case 1	103	1,110	200	15.8	3.7	68	274	1,120	79	—	7.7	3.0
Case 2	100	1,740	100	18.4	3.2	103	215	1,400	72	—	8.8	3.1
Case 3	100	715	120	2.0	3.1	206	660	1,720	92	—	8.3	3.4
Case 4	158	784	46	5.4	3.0	74	250	1,400	89	—	7.9	3.2

* As determined by RIA using ^{125}I-cholylglycylhistamine as a label.[19] Normal values: 4.5 ± 2.5 μMol/l.

Fig. 2—Higher magnification of the portal area showing abnormal shape bile ducts represented as sickle-shaped with partial occlusion of their lumina (Hematoxylin and eosin, original magnification x250).

matory cells (Fig. 1). In advanced cases, the portal fibrosis is marked extending from one portal region to the next with the formation of monolobular cirrhosis. As observed by others, the proliferating bile ductules are abnormal with stenosis and partial occlusion of their lumina (Fig. 2). Many bile ducts appear incomplete as sickle-shaped and cord-like ductules. Mild to moderate inflammatory infiltrate consisting predominantly of lymphocytes, histiocytes and plasma cells with occasional eosinophils is a constant feature. The inflammatory process appears to be located outside the bile ducts rather than within the lumina resulting in concentric fibrosis and pericholangitis (Fig. 3). Bile plugging is noted in all cases; it varies from small droplets within the canaliculi to large bile

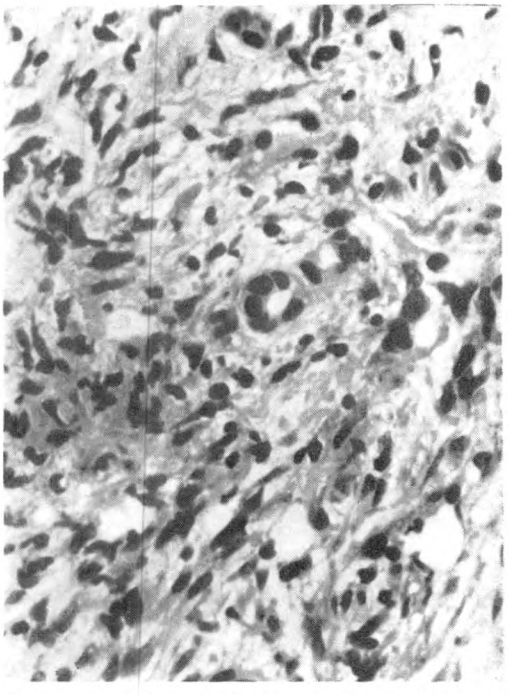


Fig. 3—Liver biopsy demonstrating marked pericholangitis (Hematoxylin and eosin, original magnification x250).

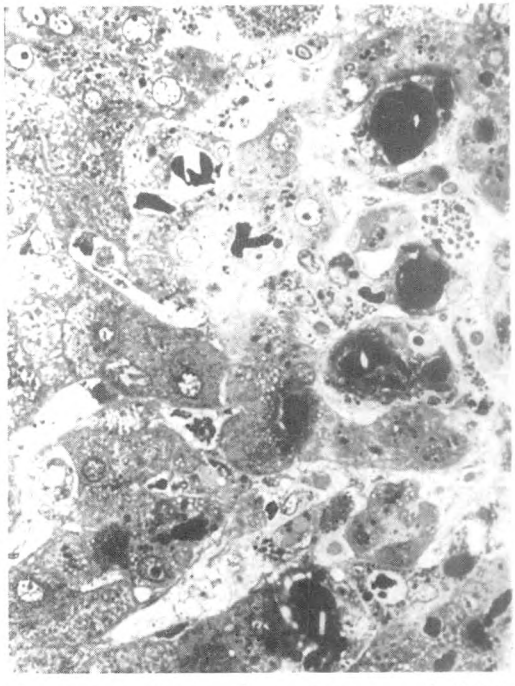


Fig. 4—Liver biopsy demonstrating marked bile plugging. One micron section (Toluidine blue, original magnification x400).

plugs involving a major portion of the biopsy (Fig. 4).

By electron microscopy the process was primarily a pericholangitis with infiltration by macrophages, polymorphonuclears and lymphocytes (Fig. 5). Focal cytoplasmic degradation with the formation of lamellar structures is observed within the cytoplasm of the proliferating bile ductules (Fig. 5). Lamellar degeneration is also observed in the portal cellular infiltrate especially the macrophages and pericytes (Fig. 6). "Bile plugging" was observed mainly in the extracellular spaces. It consists of a well delineated structure of electron dense core and fibrillar periphery (Fig. 7). Similar findings were described recently in a patient with colitis and sclerosing cholangitis.[12] Large numbers of lysozyme-like structures are observed in the hepatocytes (Fig. 8).

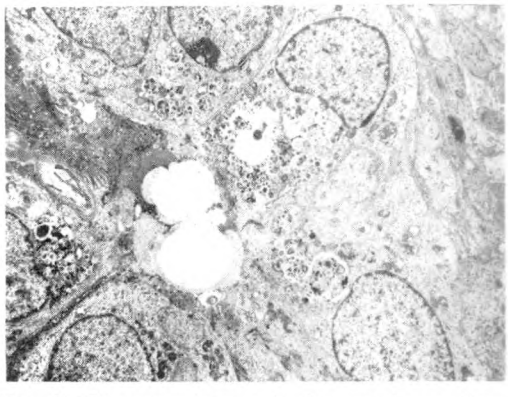


Fig. 5—Electron micrograph of a portal area showing marked cytoplasmic degradation of the bile duct epithelium (Original magnification x4,500).

Comment

The etiology of sclerosing cholangitis remains obscure. Many etiological factors have been proposed but none are proven. Low grade bacterial infection,[13] viral[14] and autoimmune disease[15,16] are among those

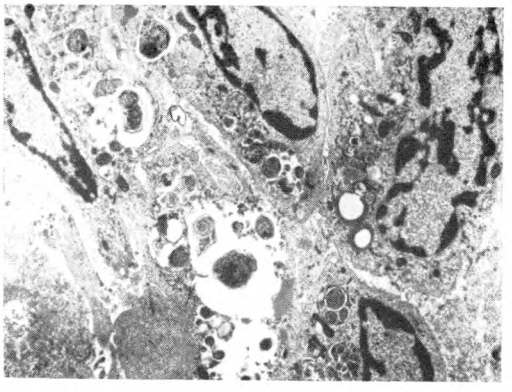


Fig. 6—Electron micrograph of the portal cellular infiltrate showing lamellar cytoplasmic degradation (Original magnification x10,400).

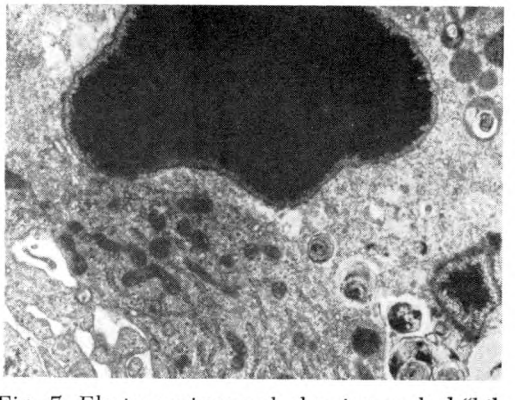


Fig. 7—Electron micrograph showing marked "bile plugging" represented as membrane-limited electron dense structures (Original magnification x18,500).

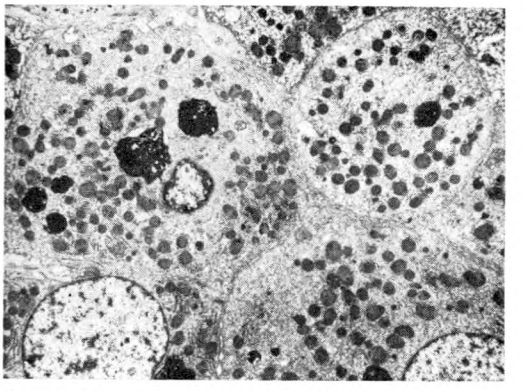


Fig. 8—Electron micrographs of hepatocytes showing increased number of lysozyme-like lipochrome granules (Original magnification x3,500).

proposed. The autoimmune theory is intriguing but most evidence supporting it is indirect. Coexistence of ulcerative colitis with sclerosing cholangitis has suggested a possible common inciting factor, although a common pathogenesis has not been proved.

A review of the clinical and laboratory data of our patients reveals several details common to all and certain differences, which may have relevance to etiology, treatment and prognosis. Common to all is the presence of ulcerative colitis, history of pruritus, absence of gallstones and the presence of bone disease. It is of great interest that the development of sclerosing cholangitis was not related to the activity of colitis and in one patient progressed relentlessly to death nine years after the onset of colitis and four years following total proctocolectomy. This is in contrast with a recent report[17] advocating colectomy for prevention and/or treatment of liver disease in patients with ulcerative colitis.

Further features common to all cases were the histologic changes observed in the liver biopsies both by light and electron microscopy. The mesenchymal proliferation involving phagocytic, fibroblastic and immunocytic cells is compatible with an immunologic type of liver injury which may attack bile duct epithelial cells. This would be in keeping with recent reports, showing cellular immune reactivity to a bile duct antigen in patients with sclerosing cholangitis.[18] The increased lysosome-like structures, seen on electron microscopy, most likely represent lipofuscin granules, which are usually seen in cholestasis and in livers from older age patients. Also, the presence of myelin fibers within hepatocytes and bile duct epithelium does not appear to be specific for the lesion as it can be observed in a variety of circumstances. In this case, narrowing of the biliary tract lumina may have caused stag-

nation leading to deposition of these myelin fibers. Another common feature to all cases and very intriguing to us, was the intense electron dense substance described above (Fig. 7). This may be a so-called bile plug but the nature of it is not definitely known. It certainly could be bile or biliary material, although there is very little in bile that would absorb enough osmium tetroxide to yield this high degree of density.

The striking elevations in serum bile acid levels and the cholestasis observed in all patients may reflect either a disturbance of transport to the liver cells or may be due to a lesion localized in the "bile-secretory" mechanisms best characterized by alteration of bile canaliculi, ductules and ducts. The injury to bile ducts may be the result of an exogenous "poison" or antigenic material from the diseased bowel of these patients. Although the HBsAg was negative in all cases, damage to bile ducts by a specific virus cannot be excluded. Whether the elevated levels of serum bile acids are important in the initiation or perpetuation of this type of injury is not known. And although it appears that the increased serum bile acids are the result of sclerosing cholangitis, further studies are needed to investigate the role of bile acids in the pathogenesis of this disease.

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Communication from Abroad

Angiography in Chronic Pancreatitis and Pancreatic Cancer*

A Critical Evaluation

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A critical "blind" evaluation of 129 randomly selected angiographic examinations was carried out including 37 control patients, 58 patients affected by proven chronic relapsing pancreatitis and 34 patients with cancer of the pancreas. In 48.5% of the control patients a completely normal angiographic picture was found. The false positives were found in 10.8% of chronic pancreatitis and in pancreatic carcinoma in 5.5% of the cases. Equivocal signs were found in 35.2%. The percentage of the false negative results in chronic pancreatitis was 34.4% (of which 8.6% were suggestive of pancreatic cancer). In pancreatic cancer positive results were seen in 70.6% of the cases. The percentage of the false negatives was 26.5% (suggestive of chronic pancreatitis); equivocal signs were found in 2.9% of these patients. Notwithstanding the not-negligible percentage of errors, angiography can be usefully employed in diagnosis of pancreatic disorders.

Since its introduction by Odman in 1958,[1] selective pancreatic angiography (S.P.A.) has become a well-established technic for evaluating the presence, extent and type of pancreatic disease. The data of angiographic literature concerning the findings in pancreatitis, however, are rather controversial.[2-10] The angiographic differentiation of pancreatitis from pancreatic cancer is also questionable,[11-13] even with the most sophisticated angiographic technics.[14-16]

The purpose of this study is to carry out a blind, retrospective analysis on a

* An abstract of this paper was read at the Eighth Meeting of the European Pancreatic Club, Toulouse, 1975.

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TALE I

ANGIOGRAPHIC FINDINGS IN EXTRAPANCREATIC ARTERIES

Patterns	Control patients	Chronic pancreatitis	Pancreatic carcinoma
Normal	94.5%	51.7% (30)	11.7% (4)
Encasement			
smooth	2.7%	8.7% (5)	14.7% (5)
beaded	—	17.3% (10)	17.6% (6)
serpiginous or serrated	2.7%	3.4% (2)	52.9% (18)
Displaced smoothly	5.4%	20.7% (12)	11.7% (4)
Occluded	—	6.8% (4)	11.7% (4)

Figures in parentheses denote number of cases.

TABLE II

ANGIOGRAPHIC FINDINGS IN INTRAPANCREATIC ARTERIES

Patterns	Control patients	Chronic pancreatitis	Pancreatic carcinoma
Normal	48.6%	1.7% (1)	—
Encasement			
smooth	35.2%	34.4% (20)	11.7% (4)
beaded	10.8%	51.7% (30)	44.1% (15)
serpiginous or serrated	2.7%	3.4% (2)	20.6% (7)
Displaced smoothly	2.7%	24.1% (14)	2.9% (1)
Occluded	—	8.7%	58.8%

Figures in parentheses denote number of cases.

series of angiographic examinations including control and pancreatic patients.

METHODS AND PATIENTS

The retrospective study included the results of 129 angiographic examinations. The radiological team (two examiners equally experienced) dealing with the retrospective evaluation of the radiograms was not informed of the fully documented final diagnosis. The interval between carrying out the angiograms and the moment of the rereading of the blind study was more than one year. On the basis of the definitive diagnosis the following groups were collected:

Control patients, 37 cases:—Patients for which successive full clinical, laboratory and radiological investigations excluded pancreatic disease. The final diagnoses, surgically confirmed, were gastrointestinal bleeding (12 cases), renal cysts and tumors (9 cases), splenic traumas (2 cases), hepatic cysts and tumors (8 cases), car-

TABLE III

ANGIOGRAPHIC FINDINGS IN CAPILLARY PHASE

Patterns	Control patients	Chronic pancreatitis	Pancreatic carcinoma
Hypovascular areas	29.7%	56.8% (33)	50% (16)
Hypervascular areas	2.7%	12.0% (7)	2.9% (1)

Figures in parentheses denote number of cases.

cinoid tumors (2 cases), miscellaneous (4 cases). Other parameters of this group were: range of age 22-48 years (mean 38); ethanol intake less than 50 gm./day; absence of chronic hepatic disease (excluding liver tumors); absence of therapy with drugs injurious to the pancreas. Furthermore none of the controls were suffering from diabetes, hyperparathyroidism, or dyslipidemia.

Patients with chronic relapsing pancreatitis, 58 cases:—Patients underwent angiographic examinations because of abdominal pains later shown to be due to pancreatitis on the basis of the following parameters: relevant serum amylase increases during acute attacks (in all patients); radiological calcifications in pancreatic area (in 41 cases) and/or other gastroduodenal radiological abnormalities (in 36 cases). Diagnosis was also confirmed during surgery by histological examination (in 47 cases). Duodenal drainage was performed in all the cases with a modification of Lagerlöf's[17] double lumen tube. The procedure for the hormonal pancreatic test[18] was as follows: after 1 C.U./kg. of (GIH) secretin and 1 IvyU./kg. of (GIH) pancreozymin given intravenously, only one 30 minute sample was collected. Collection of gastric and duodenal juice was performed separately and by manual intermittent aspiration. The following parameters were studied: 1. volume/30 min.; 2. concentration and output of bicarbonate; 3. amylase (Somogyi's method[19]), 4. lipase (Sarles', et al, method[20]); 5. trypsin and chymotrypsin (Figarella's, et al, method[21]). The lower limit of the normal range was determined by subtracting 2 standard deviations from the mean values of 45 normal subjects.

Patients with pancreatic cancer, 34 cases:—Patients underwent angiographic examinations because of abdominal pain and/or the appearance of jaundice and/or diabetes. Diagnosis was always confirmed by surgical and pathological findings.

Angiographic technic:—Selective coeliac and superior mesenteric angiography was carried out as the standard procedure in each patient. Subselective injections were done in 75% of patients. Magnification was utilized when necessary to improve visualization of pancreatic arteries (25%).

Angiographic findings:—The following parameters were considered: 1. Extrapancreatic and intrapancreatic arteries: a. normal; b. encasement; c. displacement; d. occlusion. 2. Capilliary phase: a. reduced density; b. increased density. 3. Veins: a. normal; b. compressed; c. displaced; d. occluded; e. not seen.

RESULTS

Tables I and II show the frequency of various extrapancreatic and intrapancreatic arterial abnormalities, respectively,

TABLE IV

ANGIOGRAPHIC FINDINGS IN VEINS

Patterns	Chronic pancreatitis	Pancreatic carcinoma
Normal	63.8%	35.3%
Compressed	18.9%	35.2%
Displaced	1.7%	2.9%
Occluded	8.6%	14.7%
Not seen (possibly occluded)	6.8%	11.7%

for each patient group defined on the basis of the final diagnosis.

In control patients, extrapancreatic arteries showed minimal abnormalities (about 6%), while intrapancreatic arteries were abnormal in more than 50%. Most of the abnormalities (about 35%) were smooth encasement.

In chronic pancreatitis, extrapancreatic arteries appear somewhat abnormal in about 50%, while almost all the intrapancreatic arteries show beaded encasements and displacements.

In pancreatic carcinoma only 11% of extrapancreatic arteries are normal; normality of intrapancreatic arteries was not seen. Most of the abnormalities were serrated encasement for extrapancreatic arteries and occlusion for intrapancreatic arteries.

Table III shows the frequency of the capillary phase changes in the various patient groups. Areas of reduced density were present in about 30% of control patients, in about 50% of chronic pancreatitis and in about 50% of pancreatic carcinomas. Areas of increased density were present in a small percentage of cases in all three groups.

As far as the venous abnormalities were concerned (Table IV), a pathological pattern of 37% has been found in chronic pancreatitis as well as in 65% of pancreatic cancers.

TABLE V

ANGIOGRAPHIC ACCURACY IN CONTROL PATIENTS

True negatives	48.5%
False positives for chronic pancreatitis	10.8%
False positives for pancreatic carcinoma	5.5%
Equivocal signs	35.2%

Angiographic accuracy in control patients and in chronic pancreatitis and pancreatic cancer patients, is reported in Tables V, VI and VII.

COMMENT

Our retrospective blind study shows a normality of the angiographic picture in about 50% of the control patients. Minor, equivocal alterations are found in one-third of these cases, the lesions being suggestive of chronic pancreatitis (11%) or of pancreatic cancer (5%). These false positives were mainly due to intrapancreatic artery abnormalities (Table II).

In chronic pancreatitis, concerning which the angiographic literature is characterized by marked discordant findings,[2-5] one-quarter of our cases showed equivocal alterations and in about 10%, the picture suggested cancer of the pancreas. The false negatives were seen in 1.7%. Reuter's,[4] Nesebar and Pollard's[6] percentages of false negatives results in chronic pancreatitis are conspicuously higher probably due to more equivocal angiographic signs (respectively 22% and 70%).

Alterations of the intrapancreatic arteries were more frequent than those of the extrapancreatic vessels. Moreover, these

TABLE VI

ANGIOGRAPHIC ACCURACY IN CHRONIC PANCREATITIS

True positives	65.6%
False positives for pancreatic carcinoma	8.6%
False negatives	1.7%
Equivocal signs	24.1%

TABLE VII

ANGIOGRAPHIC ACCURACY IN PANCREATIC CARCINOMA

True positives	70.6%
False negatives (positives for chronic pancreatitis)	26.5%
Equivocal signs	2.9%

patients have a clearly higher percentage of hypervascularization (12%) if compared with the controls (2.7%) or with the patients affected by pancreatic cancer (2.9%). On the other hand, the possibility of hypervascularization,[22] normal vascularization[23] or hypovascularization[3,24] in chronic pancreatitis is well known. Such heterogeneity depends on the phase of the pancreatic damage,[25] increase in vascularization being the expression of an acute stage.[10] In fact, the angiographic picture in chronic pancreatitis is related more to the duration of the disease than to the severity of the inflammation.[4]

In our patients suffering from pancreatic cancer, angiography was diagnostic or strongly suspicious in more than the two-thirds of the cases (70%). In similar retrospective studies, higher percentages have been reported: 92%,[9] 90%[12,26] 95%.[25] In false negative cases, the picture was suggestive of chronic pancreatitis except for 2% with equivocal signs. In one-third of the cases, a correct differential diagnosis between chronic pancreatitis and cancer of the pancreas could not be established. The influence of the false positive and false negative results on the differential diagnosis, together with the presence of arterial spasm, arterial dysplasia or arteriosclerotic alterations is well known in the angiographic literature.[27,28]

As far as the venous phase is concerned, the venous picture was indeed normal only in 35.3% of the cases of pancreatic cancer vs. the 63% of normality which was found in patients with chronic pancreatitis.

From the above consideration, it is clear one must establish the "diagnostic value" (D.V.)* of each angiographic sign in order to improve differential diagnosis between chronic pancreatitis and pancreatic cancer.

We considered the D.V. of the signs reliable (for the first clinical situation) when it was above 66%; on the contrary, when below 33%, it was considered reliable for the opposite eventuality (second clinical situation). The sign is considered non-reliable when between 33% and 66%.

Serpiginous or serrated encasement of intra- (D.V. 85.8%) and extrapancreatic (D.V. 93.9%) and occlusion of intrapancreatic (D.V. 87.2%) arteries have been found the sole reliable angiographic signs for malignancy. Smooth encasement and occlusion of the extrapancreatic arteries and compression or occlusion of veins were found, however, very near to the lower

* The D.V. of each angiographic sign, indicative of a particular clinical situation in comparison with another (controls vs. pancreatic disease, or cancer vs. chronic pancreatitis), is given by the following mathematical formula:

$(a + b) : 100 = a : x$, in which

a = sign's percentage in first clinical situation,

b = sign's percentage in second clinical situation,

x = "diagnostic value" of the sign.

limit of the reliability for a malignant lesion. Smooth encasement and/or smooth displacement (D.V. respectively 25.5% and 10.7%) of intrapancreatic arteries and the finding of hypervascular areas (D.V. 19.4%) have been considered reliable signs for chronic pancreatitis in the differential diagnosis with the cancer.

Conclusion

Limitations undoubtedly exist to the diagnostic accuracy of angiography[4,11,12,13,29] so that the arteriograms must be evaluated with great caution. We think, however, that the literature and our results enable us to say that angiography is a valuable addition to the available diagnostic methods. Moreover, angiography, although not always definitive, has value in the differential diagnosis between chronic pancreatitis and pancreatic cancer. Finally, as others have reported,[27,28] angiography gives useful information to the surgeon. In fact patients affected by cancer who, with angiography, are found to have invasion of extrapancreatic arteries (excluding splenic arteries), portal and mesenteric veins, three or more intrapancreatic arteries or hepatic metastases[30-32] are considered to be nonresectable.

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The Parotid and the Pancreas

VI. Clinical and Physiologic Associations Between the Pancreas and Parotid Glands

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Physiologic, experimental, and clinical studies have been presented concerning the salivary secretion in man and animals with and without pancreatic disease. Further evidence is presented that both organs tend to respond to noxious agents, to show a parallelism of secretion, and to display a glandular histologic and functional relationship which may be concordant or inverse.

Parotid-pancreatic associations are first suggested to the physician in medical school by the pathologist who describes similarities in architecture and cellular detail and by the physiologist who reveals susceptibility of both glands to similar stimulants as well as common characteristics of secretion. A clinical association has also been long noted by the pediatricians, i.e. the mumps virus attacks both organs selectively.[1] More recently, clinical associations between the parotid and the pancreas have been stressed by reports of enlargement of the parotid gland in patients with pancreatic inflammation and pancreatic cancer.[2-4] Kakizaki and his group, moreover, studying parotid secretion in response to pilocarpine in patients with and without pancreatitis, observed abnormal patterns of secretion in the latter group which he suggests are useful in the diagnosis of pancreatic disease.

This communication is the report of physiologic studies of parotid secretion as well as clinical investigations comparing parotid and pancreatic secretion in control subjects with the data of patients with pancreatic disorders.

Protocols of Study

In testing parotid secretion, fasted dogs anesthetized by I.V. phenobarbital (0.35 mg./kg.) were placed on their left side and the right parotid papilla covered with a standard saliva sampling cup. The parotid stimulant was then given and saliva was collected under oil in five-minute periods for 30 minutes. Each test was repeated

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TABLE I

PRELIMINARY PHYSIOLOGIC STUDIES OF CANINE PAROTID SECRETION USING PILOCARPINE AND URECHOLINE AS STIMULANTS

	Volume ml./5 min.	HCO_3 mEq./l.	HCO_3 mEq./5 min.	Amylase U./ml.	Amylase U./kg.
A Urecholine infusions-0.24 mg./kg./hr.					
Urecholine	7.6 ± .31	39 ± 2.9	.3 ± 0.2	.02 ± .0	.20 ± .02
Control saline	7.3 ± .41	40 ± 1.0	.3 ± .02	.03 ± .0	.23 ± .02
Urecholine	8.0 ± .10	40 ± 1.1	.3 ± .01	.03 ± .0	.24 ± .00
Secretin .06 U./kg./min.	8.1 ± .14	40 ± 2.3	.3 ± .01	.03 ± .0	.23 ± .00
Urecholine	3.9 ± .23	33 ± 1.8	.1 ± .01	.04 ± .0	.15 ± .00
Secretin 4 U./kg. S.C.	4.2 ± .26*	36 ± 1.2	.1 ± .01	.04 ± .0	.16 ± .01
Urecholine	4.6 ± .21	31 ± 1.0	.1 ± .06	.03 ± .0	.10 ± .00
CCK-PZ .06 U./kg./min.	8.1 ± .94*	42 ± 1.7*	.3 ± .02*	.03 ± .0	.23 ± .02*
Urecholine	3.1 ± .33	35 ± 1.7	.1 ± .01	.04 ± .0	.17 ± .02
CCK-PZ 4 U./kg. S.C.	4.0 ± .22*	38 ± .8	.1 ± .01	.04 ± .0	.17 ± .01
Urecholine	5.2 ± .30	49 ± 3.2	.2 ± .03	.02 ± .0	.12 ± .01
SEC + CCK-PZ .03 U./kg./min.	5.5 ± .18*	55 ± 3.1*	.3 ± .02*	.03 ± .0	.20 ± .00*
Urecholine	5.7 ± .20	29 ± 1.2	.2 ± .02	.02 ± .0	.11 ± .01
Pentagastrin 5 U./kg./hr.	5.4 ± .59	34 ± 2.3*	.2 ± .02	.02 ± .0	.12 ± .01
Urecholine	5.0 ± .38	54 ± 4.1	.3 ± .03	.02 ± .0	.14 ± .02
PGE_2 2.5 U./kg. I.V.	2.6 ± .03*	48 ± 6.0	.1 ± .01*	.05 ± .0*	.12 ± .01

TABLE I *(continued)*

PRELIMINARY PHYSIOLOGIC STUDIES OF CANINE PAROTID SECRETION USING PILOCARPINE AND URECHOLINE AS STIMULANTS

	Volume ml./5 min.	HCO_3 mEq./l.	HCO_3 mEq./5 min.	Amylase U./ml.	Amylase U./kg.
Urecholine-indomethacin	5.6 ± .03	35 ± .66	.2 ± .00	.02 ± .0	.12 ± .0
PGE_2 .1 U./kg./hr.	3.8 ± .07*	44 ± 3.07*	.1 ± .00*	.03 ± .0*	.11 ± .0
Urecholine-indomethacin	5.6 ± .03	35 ± .46	.2 ± .00	.02 ± .0	.16 ± .0
PGE_2 2.5 U./kg. I.V.	3.8 ± .10*	45 ± 1.71*	.1 ± .00*	.04 ± .0*	.16 ± .04
Pilocarpine					
0.25 mg./kg. S.C.	3.9 ± .66	68 ± 3.7	.3 ± .04	.02 ± .00	0.07 ± .0
0.24 mg./kg./hr. infusion	3.2 ± .18	63 ± 1.3	.21 ± .01	.02 ± .00	0.07 ± .0
Urecholine S.C.					
0.125 mg./kg.	1.3 ± .42	42 ± 2.6	.1 ± .01	.04 ± .01	0.14 ± .04
0.25 mg./kg.	4.3 ± .74	44 ± 3.0	.2 ± .03	.05 ± .01	0.24 ± .03
0.5 mg./kg.	4.7 ± .73	52 ± 4.7	.3 ± .05	.06 ± .01	0.31 ± .06
1.0 mg./kg.	5.9 ± .72	61 ± 2.6	.4 ± .04	.07 ± .01	0.43 ± .07
Urecholine infusion					
0.24 mg./kg./hr.	2.8 ± .18	34 ± 1.5	.1 ± .08	.04 ± .00	0.11 ± .01
0.48 mg./kg./hr.	5.7 ± .31	45 ± 2.5	.3 ± .02	.04 ± .00	0.22 ± .02
0.96 mg./kg./hr.	5.7 ± .47	57 ± 2.2	.3 ± .04	.05 ± .00	0.28 ± .02
Urecholine-in-tandem					
1 mg./kg. S.C.	6.0 ± .63	47 ± 4.4	.3 ± .02	.09 ± .01	0.74 ± .06
1 mg./kg. S.C.	6.3 ± .29	53 ± 1.8	.4 ± .04	.11 ± .02	0.93 ± .06

Asterisk indicates statistical significance at the P level of less than 5%.
Each datum represents the average of eight more experiments.

three times and average 25- to 30-minute flows, bicarbonate concentrations, bicarbonate outputs and enzyme concentration and outputs expressed as amylase units/ml. or U./30 min., were calculated. Bicarbonate was determined by Technion autoanalyzer and amylase by modified Somogyi method.

To test pancreatic function, Thomas cannulas were positioned in the duodenum of dogs weighing 20-25 mg. After ligation and divisions of the lesser pancreatic duct, pancreatic secretion data were obtained in the conscious state of animals fasting 18 hours. A standard secretion test using a 1-4 U./kg. secretin (Jorpes) I.V. bolus and an infusion test employing a stimulus of secretin (0.03 U./kg./min. Jorpes) with CCK-PZ (0.05/kg./min. Jorpes). Each test was repeated three times and the data calculated as average flow/15 min. average bicarbonate maximum as mEq./l.; average bicarbonate output as mEq./15 min. and enzyme concentration and output as mg. protein/ml. and mg. protein/15 min.

Open biopsies were performed on the parotid and pancreas following completion of the studies. Pancreotography was performed in all animals in which pancreatic function was studied. The data were calculated as mean ± S.E. A Students "t" test was used to determine statistical significance.

The initial investigations of salivary function were performed using pilocarpine (0.25 mg./kg. S.C. and 0.24 mg./kg./hr. I.V.), generously supplied by Professor Goro Kakizaki, as the stimulant. When it became apparent that pilocarpine would not be available in the United States for the experimental investigations and subsequent clinical studies, parotid responses to urecholine administered as a constant infusion (0.12 mg., 0.24 mg. and 1.0 mg./kg./hr.) and as a intravenous bolus at various dosage (0.125 mg., 0.3 mg., 0.5 mg. and 1.0 mg./kg.) were studied and compared to pilocarpine data Urecholine was found to be as potent as pilocarpine and, thus, satisfactory as a parotid stimulant.

The following physiologic agents were studied to determine the effect of each agent upon urecholine induced parotid secretion: 1. Secretin; 2. CCK-PZ; 3. 16,16-Dimethyl PGE_2; 4. indomethacin; 5. pentagastrin.

To determine the effect of pancreatic inflammation on urecholine induced parotid secretion, four dogs were subjected to 2,400 rads T.D. delivered to the pancreas on alternate days in six exposures of 400 rads each. This dose of radiation had been shown in the laboratory to produce chronic fibrotic pancreatitis with clinical pancreatic insufficiency. Biopsy of these animals at the termination of study reveal chronic fibrotic pancreatitis.

The clinical investigations were performed upon two groups of patients. Group I were 38 patients (16 with and 22 without pancreatic disease) studied using S.C. urecholine .25 mg./kg. as a stimulus with collection of saliva for 30 minutes. Group II were 52 patients (42 with and 10 without pancreatic disorder studied with similar protocol using 1 cl U./kg. secretin as the stimulant. In these patients the salivary secretory data could be correlated with the pancreatic secretin responses.

Results

The preliminary parotid secretory data are presented in Table I. It is clear that in the dog, urecholine at dosage approximate twice that of pilocarpine gives similar parotid secretory responses. A parotid stimulus of 0.25 mg./kg. subcutaneously or 0.24 mg./kg./hr. infusion was chosen as the standard stimulus in the subsequent physiologic and clinical studies.

TABLE II

SALIVARY SECRETORY DATA IN RESPONSE TO HORMONES AFFECTING PANCREATIC SECRETION

	Volume ml./5 min.	HCO_3 mEq./l.	HCO_3 mEq./5 min.	Amylase U./ml.	Amylase U./kg.
B Urecholine S.C.-0.25 mg./kg.					
Urecholine	5.4 ± .64	51 ± 4.3	.3 ± .03	.04 ± .0	.28 ± .04
Secretin .06 U./kg./hr.	4.9 ± .74	59 ± 5.7	.3 ± .04	.05 ± .0	.21 ± .05
Urecholine	5.7 ± .67	48 ± 1.9	.3 ± .03	.03 ± .0	.2 ± .04
CCK-PZ .06 U./kg./hr.	5.3 ± .67	53 ± 2.9	.3 ± .05	.03 ± .0	.2 ± .01
Urecholine	7.1 ± .72	41 ± 2.8	.3 ± .04	.16 ± .01	1.3 ± .18
PGE_2 .3 μ/kg. I.V.	6.1 ± .43*	48 ± 2.8*	.3 ± .02	.22 ± .01*	1.4 ± .15
Urecholine	5.6 ± .88	45 ± 7.1	.4 ± .03	.16 ± .01	.63 ± .06
PGE_2 .5 μ/kg. I.V.	4.9 ± .58*	64 ± 2.3*	.4 ± .05	.20 ± .02*	.59 ± .08
Urecholine	4.2 ± .69	53 ± 2.5	.3 ± .03	.07 ± .0	.29 ± .08
PGE_2 1.0 μ/kg. I.V.	2.8 ± 1.08*	63 ± 4.8*	.3 ± .11	.11 ± .0*	.31 ± .10
Urecholine	3.9 ± .43	39 ± 2.3	.2 ± .04	.14 ± .02	.51 ± .01
PGE_2 2.5 μ/kfi. I.V.	2.6 ± .37*	44 ± 2.3*	.2 ± .02	.19 ± .06*	.52 ± .19

Each datum represents the average of three to five experiments.
Data bearing asterisks indicate statistical significance at the P level of less than 5%.

Table II summarizes parotid secretory data following stimulation of the animals with hormones known to affect pancreatic secretion. The data indicate a parallelism between the effect of the hormone on both glands. Thus secretin, CCK-PZ and its analog, pentagastrin, tend to increase flow, bicarbonate concentration and enzyme output, whereas PGE_2 decreases flow, bicarbonate output, and increases bicarbonate and enzyme concentrations.

The pancreatic and parotid secretory data of eight canines before and four months after irradiation of the pancreas (2,400 rads) with shielding of the parotid are presented in Table III. The pancreatic and parotid secretion of four control dogs did not change. At the end of the experiment no histologic alterations were noted in either gland. The four dogs subjected to radiations showed significant aberrations of both parotid and pancreatic secretion. The pancreatic responses to secretin displayed statistically significant depression of flow, of bicarbonate concentration and of amylase content. The bicarbonate and amylase outputs were also statistically significantly depressed. This suppression of pancreatic secretion could be correlated with chronic inflammation and fibrosis histologically verified at the termination of the study. The parotid secretion in response to subcutaneous urecholine (.25 mg./kg.) also showed statistically significant alterations, i.e. the flow was augmented, the amylase concentration was decreased. Consequently, bicarbonate output was significantly increased but amylase output, though increased, was not changed at statistical significance. These alterations are characteristic of hypersecretion as seen in the pancreas. At the conclusion of study the parotid glands showed no histologic abnormalities.

The clinical studies with urecholine were abandoned because of: 1. severe local reactions; 2. extreme variability of data and 3. no patterns of salivary secretions could be discerned which would distinguish between the patients with and without pancreatic disorders. The clinical studies with secretin disclosed some parallelism between pancreatic and parotid secretion but reliable criteria could not be established whereby pancreatic disease could be diagnosed from alterations of parotid secretion.

Comment

Interest in parotid secretion and its relationship to pancreatic disorders was rekindled by Kakizaki and his co-workers who reported histologic and secretory alterations in the parotid of rats recovering from acute pancreatitis[5,6] as well as in dogs in whom chronic pancreatitis had been induced experimentally.[7] In these experiments, the parotid gland became atrophic and degenerative and showed hypofunction to a degree proportionate to the severity of the pancreatic lesion. Kakizaki proposed that the histologic abnormalities and functional hypersecretion of the parotid observed in these experimental pancreatic disorders derived from an "interaction" between the organs and/or similar susceptibility to damage by noxious agents.

Based upon these experimental observations Kakizaki studied parotid secretin in patients with and without pancreatic disease by collecting saliva for 25 minutes following an intramuscular injection of pilocarpine of 0.13 mg./kg. In normal subjects, he found the rate of salivary flow to be 0.204-0.707 ml./kg., the maximum bicarbonate concentration 21-48 mEq./l. and the rate of amylase secretion 694-3,348 Somogyi units/kg. Using these ranges, significant decreases in flow, bicarbonate maximum and amylase output were noted in patients with pancreatic inflammations but not in abdominal conditions not involving the pancreas.[6,8] In pancreatic cancer,

TABLE III

AVERAGE PANCREATIC AND PAROTID SECRETORY DATA FOLLOWING STIMULATION BY I.V. SECRETION (4 U./KG.) AND SUBCUTANEOUS URECHOLINE (.25 MG./KG.) BEFORE AND FOUR MONTHS AFTER IRRADIATION OF THE PANCREAS (2,400 RADS)

	#4 Control	#4 Irradiated
Pancreatic secretion-secretin 4 U./kg. I,V.		
Flow ml./15 min.	20.8 ± 1.0	3.4 ± 0.6 *
Maximum bicarbonate mEq./l.	125 ± 2.2	80 ± 3.8 *
Bicarbonate mEq./15 min.	2.6 ± 0.1	.28 ± .01*
Amylase U./ml.	17.7 ± 1.4	8.3 ± 1.3 *
Amylase U./15 min.	368.2 ± 16.1	28.2 ± 1.4 *
Parotid secretion-urecholine .25 mg./kg. S.C.		
Flow ml./min.	.83 ± .04	1.15 ± .07*
Peak flow ml./5 min.	6.5 ± 2.0	8.9 ± 2.0 *
Maximum bicarbonate mEq./l.	40.6 ± 3.3	44.4 ± 1.9
Bicarbonate mEq./5 min.	.28 ± .03	.48 ± .04*
Amylase U./ml.	.85 ± .1	.65 ± .1 *
Amylase U./5 min.	.65 ± .1	.73 ± .2

Asterisks denote statistical significance at less than the 5% level.

parotid hypersecretion was noted in three patients.[8] Moreover when he compared the parotid and secretin-pancreozymin data obtained in the same group of patients, the salivary test was simpler and more reliable for the detection of pancreatic disease than the pancreatic secretory data.[6,8]

The physiologic studies described in his communications disclose secretory responses to pilocarpine, urecholine and the gastrointestinal hormones in accordance with previous reports.[9-12]

The study of salivary secretion, following irradiation of the pancreas, implies an interglandular relationship quite different from that suggested by Kakizaki. As the pancreas became chronically inflamed by the irradiation, underwent fibrosis and atrophy and disclosed suppression of pancreatic flow, bicarbonate and enzyme, the parotid underwent hypertrophy and displayed hypersecretion of fluid and electrolyte but not enzyme protein. This experimental model appears akin to the clinical classes of pancreatic cancer with parotid hypersecretion described by Kakizaki.[7] These parallel phenomena may be explained upon the basis of trophic feedback mechanisms set up in response to organ injury. Thus, disease or noxious processes affecting the pancreas induce release of hormones stimulating hypertrophy, hyperplasia and regeneration within that organ. The parotid, being histologically similar to the pancreas, would then respond to these trophic feedback mechanisms. If this be the case, the effect of disease within the pancreas, would be twofold: first histologic and secretory responses parallel to those observed in the pancreas as a result of parotid injury by the agents noxious to the pancreas; second and opposing the first effect, the hypertrophy of the parotid in response to trophic feedback mechanisms released by the deteriorating pancreatic parenchyma.

If these hypotheses are correct, the secretory changes in the parotid and pancreas observed in pancreatic pathologies might not parallel each other and might not be in accordance with the severity of disease within the pancreas. Indeed, either

factor may predominate or both, equal in opposing direction, may nullify each other, so that the secretory capacity of the parotid may increase, be unchanged, or decrease with decreasing pancreatic function in pancreatic disorders. These considerations may very well explain the inability of the present studies to disclose abnormal patterns of parotid secretion in patients with pancreatic disease. In all fairness, there remains the question whether the difference in parotid stimulus could account for the disparate results reported by Kakizaki, et al[5,7] and the present studies.

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Mechanism of the Pancreas-parotid Gland Interaction

An Experimental Study In Parabiotic Rats

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In order to elucidate the mechanism of interaction between the pancreas and parotid gland, male Wistar rats of the same litters were used to produce parabiotic pairs. Six pairs which survived the procedure more than 30 days were available for experimentation. In one of each pair of rats, acute pancreatitis was induced. Amylase concentration in the sera, pancreas and parotid glands in these rats was estimated and histocytological studies of these organs were performed. The following results were obtained: 1. The serum amylase level was elevated in the rats with experimentally induced pancreatitis. It was slightly elevated in the rats without pancreatitis. 2. Organ amylase concentration in the pancreas and parotid gland was reduced in the rats with and without pancreatitis. The reduction of pancreas tissue amylase in the rats without pancreatitis was slight and insignificant. 3. In light microscopy, the pancreas in the rats without pancreatitis was not significantly altered compared to that of the control rats. The parotid gland in the rats without pancreatitis showed apparent atrophic degenerative changes, which were less severe than in the rats with pancreatitis. Electron microscopy revealed that the pancreas in rats without pancreatitis showed similar findings with those of the control rats. In the parotid gland, the findings in the rats without pancreatitis were less severe, but similar to those in the rats with pancreatitis. A humoral transmission mechanism is participating in the development of an interactive response between the pancreas and parotid gland.

The presence of a remarkably intimate interaction between the pancreas and parotid gland has been demonstrated both experimentally and clinically by Kakizaki, et al.[1-12] The present study was done to elucidate the etiologic mechanism of this pancreas-parotid gland interaction and particularly to search for a possible humoral mechanism for the phenomena previously described.

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Materials and Methods

Male Wister rats of the same litters were used, weighing 180-250 gm. Two rats

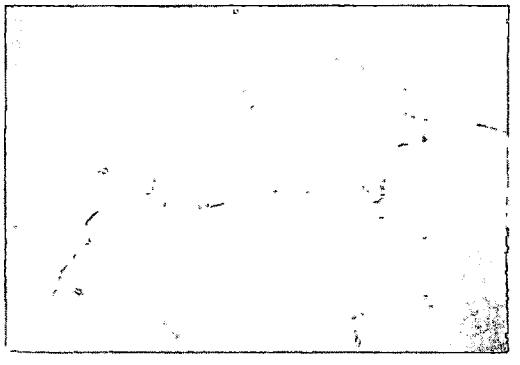


Fig. 1—Production of parabiotic rat.

were anesthetized using ether and shaved from the inguinal region over the lateral side of the trunk to the neck. A straight skin incision was made extending from the inguinal region to the scapula and a skin strip 1-2 cm. wide was resected along the line of incision. The animals were placed in the prone position and the skin of the back wound of each animal was approximated to the other with a running suture. Then the animals were placed in the supine position. To promote granulation tissue formation, the muscle layer of the lateral abdominal and chest wall wounds was incised, taking care not to enter the thoracic or abdominal cavity. The muscle and subcutaneous layers were then closed and finally the skin of the abdominal wall of the two rodents was approximated with a running suture. A stitch was placed in the tail portion to reinforce fixation. These parabiotic animals frequently die or have wound dehiscence within three weeks after operation. Our experiment was performed in six pairs of rats (Fig. 1) which survived more than 30 days after operation and showed complete healing of their wounds.

Control animals:—Three pairs of parabiotic rats fasting 12 hours were used. Under deep ether anesthesia, laparotomy was made and blood samples were obtained from the abdominal inferior vena cava for amylase measurement. Then the pancreas and parotid glands were resected and fat and blood vessels were excised as completely as possible. After washing with chilled physiological saline to remove adhering blood, the organs were again washed with chilled distilled water. Part of each gland was used for tissue amylase determination and the rest of the organ for light and electron microscopic investigation.

Production of acute pancreatitis:—Three pairs of parabiotic rats were used. In one rat of each pair, the common bile duct was ligated with a fine silk suture at the orifice into the duodenum (Block's method[13]). Ninety-six hours after operation, the rats were fasted for 12 hours and re-operated upon under deep ether anesthesia. As in the control animals, blood samples were aspirated for estimation of serum amylase and the pancreas and parotid glands were excised for tissue amylase determination and histo-cytological evaluation.

Amylase measurement:—Serum amylase activity was measured by the Caraway method.[14] For measurement of tissue amylase, the pancreas and parotid glands obtained were immediately homogenized under refrigeration in a Potters homogenizer with 10 ml. chilled distilled water. The specimen was then lyophilized to obtain pancreatic and parotid powder. Ten milligrams of the powder were dissolved in 5 ml. Tris-HCl buffer (pH 8.0) and the amylase activity of this solution was measured by the method of Caraway.[14] The amylase activity was expressed as the unit per mg of the lyophilized powder (U/mg).

Light and electron microscopic examination of the pancreas and parotid glands:—The pancreas and parotid glands were treated with 3% glutaraldehyde solution (pH 7.3) after the method of Sabatini, et al[15] at 4° C for three hours. After prefixation, the tissue was washed in several

TABLE I

SERUM AMYLASE

Parabiotic rat no.	Control group (U.)		Parabiotic rat no.	Experimental group (U.)	
	Group A rat	Group B rat		Rat with pancreatitis	Rat without pancreatitis
1	1,302	1,536	4	1,970	1,556
2	1,302	1,630	5	2,006	1,712
3	1,443	1,196	6	2,123	1,654
Average	1,349	1,454	Average	2,033	1,641

TABLE II

ORGAN AMYLASE LEVEL IN THE PANCREAS

Parabiotic rat no.	Control group (U./mg.)		Parabiotic rat no.	Experimental group (U./mg.)	
	Group A rat	Group B rat		Rat with pancreatitis	Rat without pancreatitis
1	154.0	158.8	4	28.0	119.6
2	129.2	178.4	5	11.4	94.8
3	124.0	93.9	6	13.7	123.4
Average	135.7	143.7	Average	17.7	112.6

changes of isotonic phosphate buffer solution and was postfixed for two hours in an ice cold (4° C) solution of 1% OsO4 buffered at pH 7.3 according to the method of Millonig.[16] The fixed material was dehydrated rapidly with ethanol series, and embeded in Epon 812.[17] Before preparing ultrathin sections, 1μ-thick sections were cut with glass knives and stained with toluidine blue for light microscopy. A double-staining technic, using uranyl acetate and lead citrate, was applied to the ultrathin sections on the grids. Sections were examined and photographed with an HU-12 or a JEM 100B electron microscope at an accelerating voltage of 75 or 80 kV. In addition, other sections stained with hematoxylin and eosin were made for light microscopic examination.

RESULTS

Serum amylase levels are given in Table I.

Control group:—The rats with a right-sided wound are designated as Group A rats and those with the wound on the left side as Group B rats. The serum amylase level ranged from 1,302 to 1,443 U. (mean 1,349 U.) in the Group A rats and from 1,196 to 1,630 U. (mean 1,454 U.) in the Group B rats. Thus, in both groups, the serum amylase level was approximately the same.

Experimental group:—In the rats with experimentally-induced acute pancreatitis, the serum amylase level averaged 2,033 U. (range 1,970-2,123 U.) while in their parabiots without pancreatitis, it averaged 1,641 U. (range 1,556-1,712 U.). Thus the

TABLE III

ORGAN AMYLASE LEVEL IN THE PAROTID GLAND

Parabiotic rat no.	Control group (U./mg.)		Parabiotic rat no.	Experimental group (U./mg.)	
	Group A rat	Group B rat		Rat with pancreatitis	Rat without pancreatitis
1	289.2	234.0	4	58.2	167.0
2	246.0	289.4	5	68.5	156.0
3	233.6	268.0	6	—	—
Average	256.3	263.9	Average	63.4	161.4

serum amylase level was higher in the first group with pancreatitis.

Comparison of the serum amylase levels in the control and experimental animals revealed that it was elevated in the experimental animals. The serum amylase level was most elevated in the experimental animals with acute pancreatitis.

Pancreatic tissue amylase levels are summarized in Table II.

Control group:—The amylase level in the pancreas ranged from 124.0-154.0 U./mg. (mean 135.7 U./mg.) in the Group A animals. In Group B rodents, it averaged 143.7 U./mg. (range 93.9-178.4 U./mg.). Thus the tissue amylase level in the pancreas was of the same order in the control parabiots.

Experimental group:—The amylase level in the pancreas ranged from 11.4-28.0 U./mg. (mean 17.7 U./mg.) in the animals with acute pancreatitis while it ranged from 94.8-123.4 U./mg. (mean 112.6 U./mg.) in the animals without pancreatitis. Thus the former group showed a significantly lower level.

In the rats with experimentally-induced pancreatitis, the amylase level in the pancreas was markedly reduced in comparison with those in the control group. It was slightly reduced in the parabiots of pancreatitis rats when compared to the control animals but the difference was not statistically significant.

Parotid tissue amylase levels are presented in Table III.

Control group:—The amylase level in the parotid gland averaged 256.3 U./mg. (range 233.6-289.2 U./mg.) in Group A animals while that in Group B varied from 234.0-289.4 U./mg. (mean 263.9 U./mg.).

Experimental group:—The amylase level in the parotid gland ranged from 58.2-68.5 U./mg. (mean 63.4 U./mg.) in animals with pancreatitis. In the animals without pancreatitis it was far more elevated with a mean of 161.4 U./mg. range 156.0-167.0 U./mg.).

The amylase level in the parotid gland was significantly reduced, thus, in the experimental animals with and without pancreatitis compared to control parabiotic rodents.

Light microscopic findings:—Figure 2 shows the normal histologic morphology in the pancreas of the control parabiotic rat. The findings are similar to those observed in normal rats fed routinely. There was no difference in the pancreatic histology between the control A and B groups. In the experimental animals, those with experimentally induced pancreatitis showed mor-

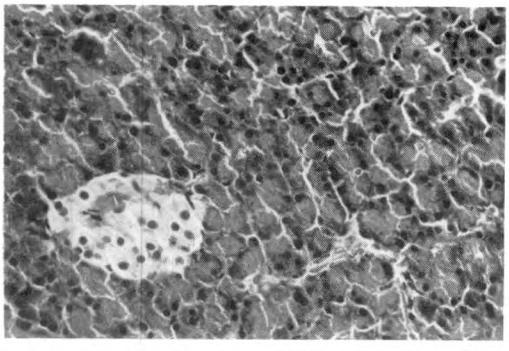


Fig. 2—Photomicrograph of the pancreas of a control rat (Hematoxylin and eosin, original magnification x200).

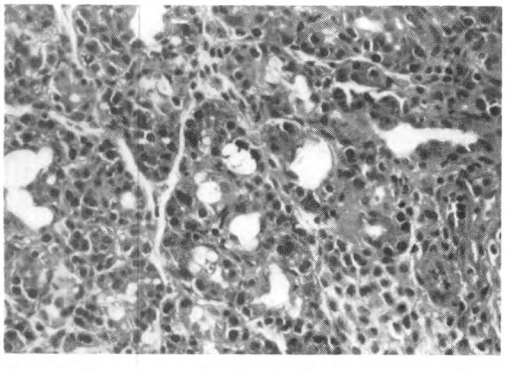


Fig. 3—Photomicrograph of the pancreas of rat with experimentally induced pancreatitis in experimental group. There are marked atrophy of acinar cells, dilatation of the ducts, disorderly arrangement of acinar cells, disappearance of zymogen granules (Hematoxylin and eosin, original magnification x200).

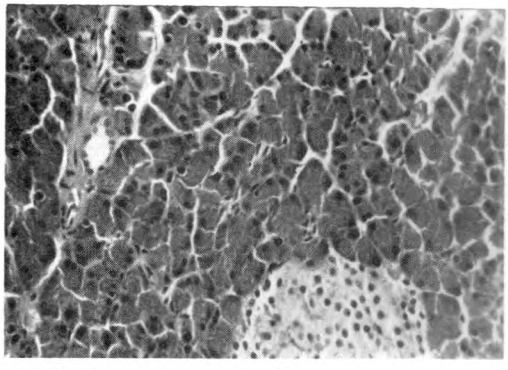


Fig. 4—Photomicrograph of the pancreas of a rat without experimentally induced pancreatitis in experimental group.

The histological picture is almost similar to that in the control rats (Hematoxylin and eosin, original magnification x200).

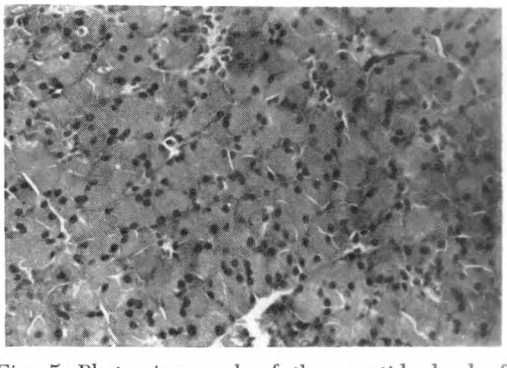


Fig. 5—Photomicrograph of the parotid gland of a control at (Hematoxylin and eosin, original magnification x200).

phologic alterations illustrated in Figure 3. There was marked atrophy of acinar cells, dilatation of the ducts, disorderly arrangement of acinar cells, disappearance of zymogen granules and exudation into the interstitial tissues. Exudation in the acini and surrounding fatty tissues, vacuolization of acinar cells, an appearance of fine granular fat droplets within the acinar cells and cellular infiltration were of slight to moderate severity. In the other paired parabiotic rat, in which experimental pancreatitis was not induced, the pancreas showed a histological picture similar to that in the control rats (Fig. 4). In parabiotic rats in which acute pancreatitis was experimentally induced in one of the paired rats, the pancreas in the other rat showed almost no histological changes.

Figure 5 shows the histological picture of the parotid gland of a control rat. It is similar to that of a normal rat. The parotid gland in the rat with acute pancreatitis showed marked atrophic degenerative changes of the acinar cells. The normal acinar structure present in the control rats was lost and the arrangement of the acinar cells was quite disorderly. Zymogen granules were frequently missing (Fig. 6). The

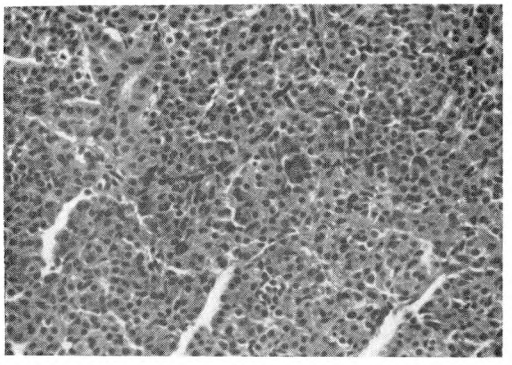


Fig. 6—Photomicrograph of the parotid gland of a rat with pancreatitis.

Atypical arrangement of acinar cells, narrowing of the acinus and disappearance of zymogen granules are markedly noticed (Hematoxylin and eosin, original magnification x200).

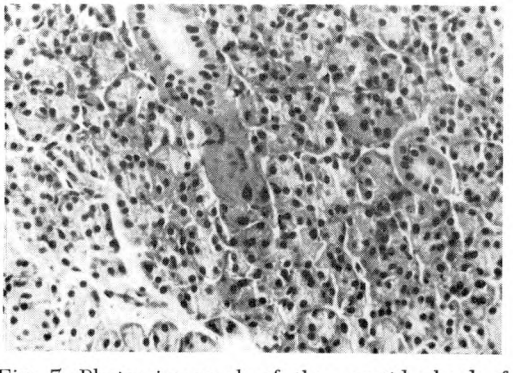


Fig. 7—Photomicrograph of the parotid gland of a rat without pancreatitis.

This shows a less severe, but similar histologic pattern to that of the rat with pancreatitis (Hematoxylin and eosin, original magnification x200).

parotid gland in the parabiotic pair showed a less severe but similar histologic pattern to that of its mate with pancreatitis (Fig. 7). Thus, atrophic degenerative changes of the parotid gland were demonstrated in both parabiotic rats in which acute pancreatitis was induced.

Electron microscopic findings:—Figure 8 shows an electron micrograph of the pancreas in the control rat. Other than the

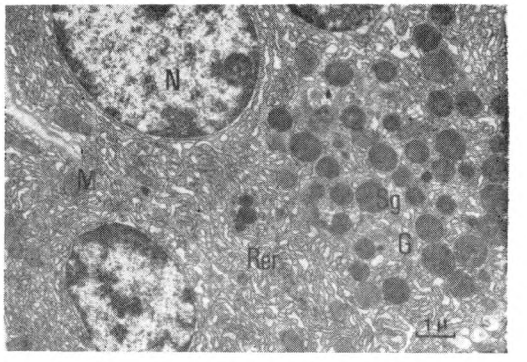


Fig. 8—Electron micrograph of the pancreas in a control rat. The granular endoplasmic reticulum is slightly dilated (Original magnification x6,000).

Sg:Secretory granule. N:nucleus. G:Golgi apparatus. M:Mitochondria. Rer:Granular endoplasmic reticulum.

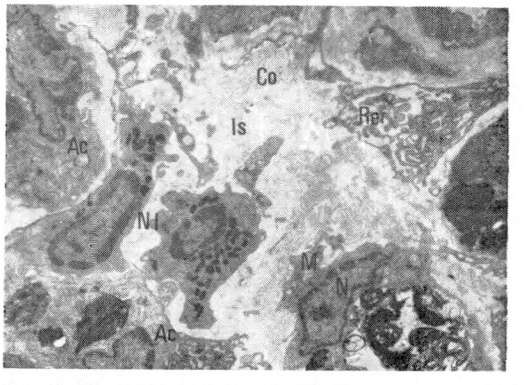


Fig. 9—Electron micrograph of the pancreas in a rat with experimentally induced pancreatitis.

Atrophy and necrosis of the acinar cells, edema and proliferation of the connective tissue in the interstitial tissue, infiltration of inflammatory cells and marked reduction in secretory granules in the acinar celles are noted (Original magnification x3,000) Co:Collagen fiber. Is:Intercellular space. Nl:Neutrophil leukocyte. Ac:Acinar cell.

granular endoplasmic reticulum being slightly dilated, the findings were almost identical with those in the normal rats. In the experimental group, the pancreas of the rat with acute pancreatitis showed atrophy and necrosis of the acinar cells,

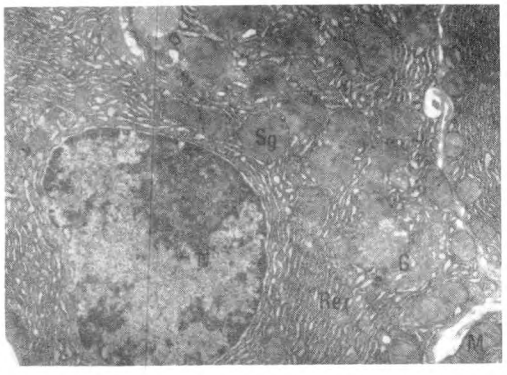


Fig. 10—Electron micrograph of the pancreas in a rat without experimentally induced pancreatitis.

Somewhat dilated granular endoplasmic reticulum is noted (Original magnification x9,000).

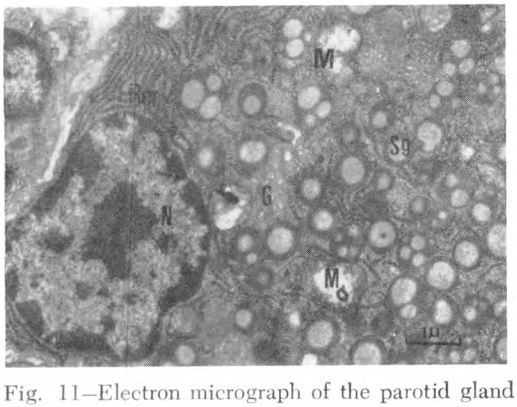


Fig. 11—Electron micrograph of the parotid gland in a control rat.

Some morphological changes in the secretory granules are present (Original magnification x9,000).

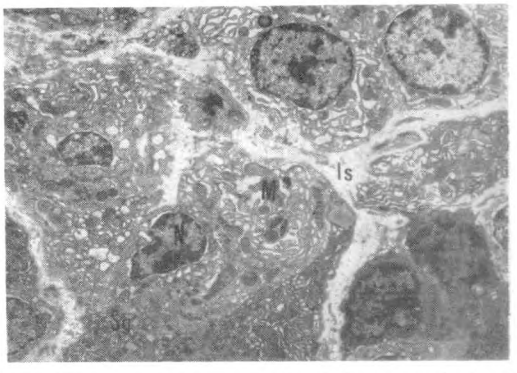


Fig. 12—Electron micrograph of the parotid gland in a rat with experimentally induced pancreatitis.

Atrophy of the acinar cells, interstitial edema, irregular nuclear border, dilatation of the granular endoplasmic reticulum and disappearance of the granules were markedly noted (Original magnification x3,000).

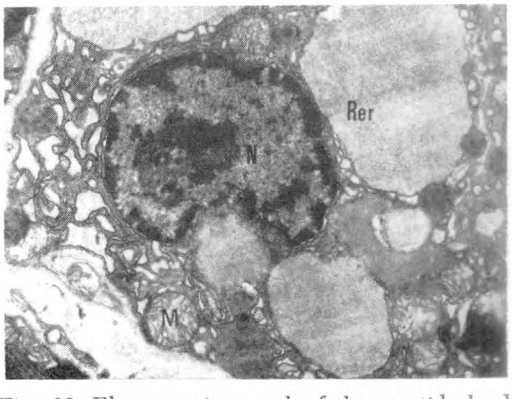


Fig. 13—Electron micrograph of the parotid gland in a rat without experimentally induced pancreatitis.

The dilatation of the granular endoplasmic reticulum is particularly pronounced and there is retention of less electron dense materials in the vesicular lumina (Original magnification x9,000).

edema and proliferation of the connective tissue in the interstitial tissue, infiltration of inflammatory cells, marked reduction in secretory granules in the acinar cells, dilatation and disappearance of the lamellar arrangement of the granular endoplasmic reticulum (Fig. 9). In the parabiotic rat, electron microscopy of the pancreas showed somewhat dilated granular endoplasmic reticulum (Fig. 10) but except for this finding, morphology was almost the same as the control rat. In short, electron microscopy of the pancreas in parabiotic rats revealed that after acute pancreatitis had been induced in one, the other rat showed no remarkable changes in the pancreas.

Figure 11 illustrates the parotid obtained from a control rat. Some morphological changes in the secretory granules were

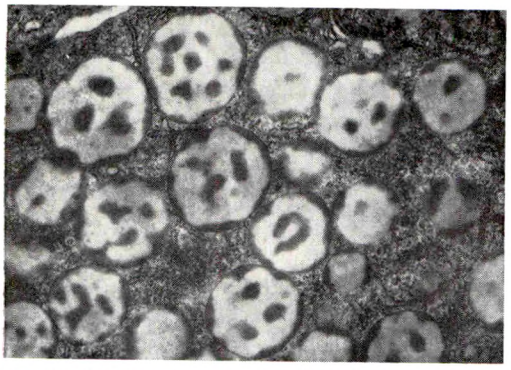


Fig. 14—Electron micrograph of the parotid gland in a rat without pancreatitis.

There are considerable morphological changes in the cells containing secretory granules. (Original magnification x21,000).

present but in general the findings were almost identical with those of the normal rat. In the experimental group, the parotid gland of the rat with acute pancreatitis revealed the electron microscopic changes as shown in Figure 12: Atrophy of the acinar cells, interstitial edema, irregular nuclear border, condensation of chromatin, dilatation of the granular endoplasmic reticulum, shift of the ribosome as in the vesicular lumina and disappearance of the granules. In the paired rat, the electron microscopic changes of the parotid gland were similar. The dilatation of the granular endoplasmic reticulum was particularly pronounced and there was retention of less electron dense materials in the vesicular lumina (Fig. 13). In the cells containing secretory granules, there were considerable morphological changes (Fig. 14). In summary, when acute pancreatitis was induced in one of the parabiotic rats, the parotid gland in the rat with pancreatitis as well as in the partner rat without pancreatitis showed similar electron microscopic pathologies.

Comment

During the last seven years, we have reported a series of experimental and clinical studies concerning the interrelationship between the pancreas and parotid gland. We have demonstrated experimentally that after a pancreatic lesion is induced, the parotid glands shows atrophic degeneration and hypofunction with diminutions in volume, amylase content and maximal bicarbonate concentration of the parotid saliva. Furthermore, with the recovery of the pancreatic lesion, the parotid glands displayed morphological as well as functional recovery[1-6]. Conversely, it was demonstrated that with impairment of the parotid glands, the pancreas also was slightly influenced.[7] These findings were applied clinically to diagnose with accuracy pancreatic pathology on the basis of parotid saliva analysis. Moreover, in man, we were able to show that function of the parotid gland was reduced in pancreatic pathologies,[8-12] a finding in accordance to the experimental data in the present study. Recently Grimmel, et al[18] reported that amylase concentration in the parotid saliva was significantly reduced in patients with chronic pancreatitis compared with normal subjects and Descos, et al,[19] comparing human whole saliva in normal subjects with saliva in patients with chronic pancreatitis, noted basal salivary secretion flow, bicarbonate concentration and amylase levels were lower than in normal subjects; both studies comparable to our results.

A major goal of our study is to clarify the mechanism of interactive response between the pancreas and parotid gland. Initially, we decided to determine whether the interaction between the two organs is due to nervous or humoral transmission. As our experimental method, we utilized parabiosis[20] which has often been used to study and is useful in demonstrating hormonal mediation. In producing the parabiotic condition, attention was paid to avoid communication between the abdominal cavities of the two rats. If this occurs,

acute pancreatitis produced in one rat would directly affect the pancreas of the other rat. Many rats died and ulceration or dehiscence of the wound often occurred within two to three weeks after production of the parabiosis. Therefore, only six pairs of rats survived more than 30 days and could be used in the study.

The serum amylase level was elevated not only in the rats with pancreatitis but also in the partner rats without pancreatitis when compared with the control rats. These findings suggest that when acute pancreatitis is induced in one of the parabiotic rats, this affects the paired rat by way of humoral transmission resulting in elevation of serum amylase.

Amylase concentration in the pancreatic tissue was much less in the rats with acute pancreatitis compared with the control rat. It was only slightly reduced in the rats without pancreatitis, the difference statistically insignificant. In the parotid gland, on the other hand, amylase concentration was significantly reduced in rats with and without pancreatitis compared to the control rats. Induction of pancreatitis in one of the parabiotic rats may affect the parotid gland of the same rat as well as the partner rat by presumed humoral transmission, reducing tissue amylase concentration.

Light microscopic examination revealed no significant change in the pancreas of rats without pancreatitis compared to the control rats. The parotid gland tissue in these animals was found to show a less severe but similar change to that in the rats with pancreatitis. Electron microscopically, the pancreas in the rats without pancreatitis showed a change similar to that in the control animals. The parotid glands of the rats without pancreatitis showed almost similar pathological electron micrograms as those in the rats with pancreatitis. When acute pancreatitis is induced, a substance which affects the parotid glands both functionally and histocytologically by humoral transmission may thus be produced.

Recently we performed cystojejunostomy in two patients with pancreatic cysts, pancreaticoduodenectomy in two patients with cancer of the duodenal papilla and cancer of the intrapancreatic bile duct, respectively, and side-to-side pancreaticojejunostomy in two patients with pancreaticolithiasis. All of these showed reduced parotid gland function preoperatively. Follow-up studies in the late postoperative period revealed that parotid gland function returned to normal in four and was abnormally elevated in one patient. In one case of cancer of the intrapancreatic bile duct, it was reduced.[12] In these procedures drainage of the pancreatic duct or cyst into the intestine produces symptomatic relief and, hypothetically, improvement of pancreatic function. It is presumed that parotid gland function was restored or elevated in association with the recovery of pancreatic function. Such a supposition implies that the human pancreas may release a substance which affects the parotid gland by humoral transmission.

In the literautre, the excretory mechanism of the parotid gland is described as controlled by autonomic nerves.[21, 22] This was unanimously accepted until the influence of gastroentestinal hormones on the secretory function of the salivary glands was actively investigated.[22-27] This experiment suggests that a substance which affects the parotid gland by humoral transmission is produced when there is pancreatic injury. Further study to identify this substance affecting parotid gland is in order.

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Clinical Vignette

Blood Kallikrein

Kinin System in Acute Pancreatitis

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Three chief components of the kallikrein-kinin system (kallikrein, kininogen, kininase) were studied in the blood of 42 patients with acute pancreatitis. Significant increase in content of kallikrein, decrease in level of kininogen, and increase of kininase activity were observed. The highest values for kallikrein, kininogen and kininase activity were found in patients in whom acute pancreatitis was accompanied by hemodynamic changes.

In spite of multiple investigations, the pathogenetic aspects of acute pancreatitis are still unclear. An essential role has been ascribed to the kinin's active humoral substances.[2, 1-4] The possible role of kinins in the development of acute pancreatitis is suggested from their high biological activity, particularly the increase in capillary permeability they induce and the pain they provoke.[5, 6]

Previous studies have been based on investigations of the separate components of the kinin system. The work here presented involved a complex study of the blood content and activity of the three major components of the kinin system: total kallikrein activity, kininogen content and kininase activity. These components reflect the principal phases of kinin production and destruction. The investigation of these components of the kinin system were conducted on patients with acute pancreatitis.

From the First Moscow Medical Institute, I. Sechenov.
* Deceased

Material and Methods

A total of 42 patients with acute pancreatitis ranging in age from 27-82 years were examined. The sex distribution was 34 women and eight men. The patients were observed in the Surgical Department of Moscow Hospital N 20.

On admission the patients had pain in the epigastric zone. In half the cases there was persistent nausea and vomiting. In nine patients there were hemodynamic changes consisting of tachycardia, decreased systolic and diastolic blood pressure and decreased central venous pressure. The fall in arterial blood pressure amounted to 30-40% from the initial level. In the early hours after onset, hyperamylasuria (from 118-2,040 units) was found in 10 patients and leucocytosis (9,000-11,000) in all patients.

The diagnosis of acute pancreatitis was based on clinical observations, results of treatment (Trasylol, analgesics, antibiotics) at operation (10 cases) or autopsy (three cases).

The components of the kinin system were studied in the majority of the patients on the first and second days after onset of the disease. Blood was collected from the antecubutal vein by siliconated needles and placed in polyethylene tubes in the cold (4° C). All blood studies were conducted in polyethylene or siliconated tubes and all the components of kinin system tested for in heparinized plasma (3-5 U./ml.). Plasma kallikrein was determined by the method of Surovikina,[7] kininogen by Diniz' modification of the method of Paskhina and Egorova[8] and kininase activity by Erdos' modification of the method of Surovikina.[9] The quantitative kinin test was conducted with the use of original equipment designed for isolated organ registration by the superfusion method.[10]

Results

The results are summarized in Table I. In the group of healthy persons[6] the values were: (mean ± SE): total kallikrein, (mg./ml.) 1.15 ± 0.21; kininogen, (μg./ml.) — 4.62 ± 0.32; kininase activity, (μg./ml./min.) — 0.83 ± 0.10.

In patients with acute pancreatitis (42) the values were: kallikrein, 1.79 ± 0.16 μg./ml.; kininogen, 4.03 ± 0.22 μg./ml. and kininase activity of 1.04 ± 0.04 μg./ml./min.

The highest values for kallikrein 2.64 ± 0.27 μg./ml.) and kininase activity in the blood (1.32 ± 0.07 μg./ml./min.) were in the group of patients (9) in whom acute pancreatitis was accompanied by hemodynamic disorders. In this group of patients the lowest content of kininogen (3.40 ± 0.16 μg./ml.) was found.

In order to make more clear the interconnection between the levels of the components of the kinin system and hemodynamic changes in patients with acute pancreatitis, the same values were determined in a group of patients without hemodynamic changes. Kallikrein, (1.55 ± 0.17 μg./ml.); kininogen, (4.17 ± 0.30 μg./ml.) and kininase activity of blood, (0.96 ± 0.08 μg./ml./min.) did not differ significantly from the same indices in healthy persons. In patients with acute pancreatitis without hemodynamic changes, the content of kininogen (4.17 ± 0.30 μg./ml./min.) had a tendency to decrease and the kininase activity of blood (0.96 ± 0.08 μg./ml./min.) to increase.

Comparison of the indices of the kinin system with inflammatory indices—leucocytosis, erythrocyte sedimentation and urinary diastase (amylase) failed to show correlation.

Discussion

The data obtained suggest that significant changes in content and activity of the three basic components of the kinin system (kallikrein, kininogen and kininase activity of the blood) occur in patients with acute pancreatitis. Simultaneous increase of the level of kallikrein and decrease in the level of kininogen in the blood of patients with acute pancreatitis indicate a significant increase in formation of kinins. Increase of kininase activity appears to be a compensatory reaction to intensification of kinin production.

Maximal activation of the blood kinin system was noted in patients with acute pancreatitis complicated by hypotension.

In patients with acute pancreatitis without hemodynamic changes, the kinin indices did not differ significantly from healthy persons.

The role of the kinin system in the development of acute pancreatitis may be postulated to be as follows: Different etiological factors lead to partial cytolysis of

TABLE I

	Control	Acute pancreatitis	With hemodynamic disorders	Without hemodynamic disorders
		Kallikrein μg./ml.		
Number of cases	10	42	9	33
Mean	1.15	1.79	2.64	1.55
± SE	0.21	0.16	0.27	0.17
P		0.05	0.05	
		Kininogen μg./ml.		
Number of cases	10	42	9	33
Mean	4.62	4.03	3.40	4.17
± SE	0.32	0.22	0.16	0.30
P		0.05	0.05	
		Kininase activity μg./ml./min.		
Number of cases	10	42	9	33
Mean	0.83	1.04	1.32	0.96
± SE	0.10	0.04	0.07	0.08
P		0.05	0.05	

pancreatic cells. This is accompanied by the release of some intracellular enzymes, cytokinase among them. Cytokinase promotes activation and significant increase of kallikrein of the pancreas together with other proteases. These act as mediators of hyperproduction of tissue kinins. The latter intensify the pathological process in the pancreas by increasing the permeability of the capillaries and edema formation. They also intensify pain. At a certain stage of the pathological process, a "rupture" of tissue barriers takes place with release of a great deal of kallikrein and free kinins formed in the pancreas. Tissue kallikrein, affecting the kininogen of the plasma, promotes a larger output of free kinins and leads to progressive hypotension and collapse. The latter is supported by our finding the highest degree of activation of kinin in those patients in whom acute pancreatitis was accompanied by hypotension.

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Clinical Vignette

Spontaneous External Biliary Fistula in a Patient with Heroin Addiction

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Spontaneous external biliary fistula, once common, is now a rare clinical entity. A patient with this lesion is described and attention is drawn to the fact that this rare condition is still being seen in certain patients with neglected cholecystitis. Heroin addiction was thought to have modified his response to gallbladder disease and contributed to the perforation. Diagnosis was suspected on physical examination and confirmed by spontaneous discharge of stones and fistulogram.

Perforation of the gallbladder, secondary to cholecystitis and cholelithiasis, is a well-known but infrequent complication of biliary tract disease.[1-2] Such perforations may form fistulas with an adjacent viscus or rupture into the peritoneal space. External cutaneous biliary fistula, another rare complication of cholecystitis, was common before 1900 but with the advent of biliary surgery, has almost become nonexistent in the United States.[3] The purpose of this report is to present a case of spontaneous external biliary fistula in a male heroin addict, and review the pertinent literature of this medical curiosity.

Case Report

A 45-year old man was admitted to the Phoenix Veterans Administration Hospital because of a tender, reddened area in the right upper quadrant of his abdomen. This had developed over a two-week period. The patient had been a "main-line" heroin addict for ten years. Twenty years previously he had had a subtotal gastric resection to correct an obstructing duodenal ulcer. This procedure was complicated by an abdominal abscess, which was surgically drained. Physical examination revealed a well-nourished white male, with extensive needle scars on both forearms. The vital signs were normal. A tender, fluctuant, red mass was present in the right upper quadrant at the lateral aspect of the surgical scar. No other abnormalities were detected.

Before incision and drainage of the abscess could be done, it ruptured, discharging necrotic material and four yellow-green gallstones. The patient refused definitive surgery and was discharged. He returned eight months later, complaining of chronic drainage from the fistula (Fig. 1). He had expressed several stones from it. He denied any pain or jaundice. He had continued his heroin habit. A fistulogram showed the connection between the skin and the gallbladder (Fig. 2). The cystic duct and retained sutures from the previous gastric surgery are seen. The gallbladder is filled with radiolucent stones. Culture of the drainage grew staphylococcus aureus and *E. coli*. Liver functions were normal and the upper gastrointestinal series showed a Billroth II gastric resection. At surgery, dense adhesions were encountered around the gallbladder and at the site of the previous gastric surgery. The gallblad-

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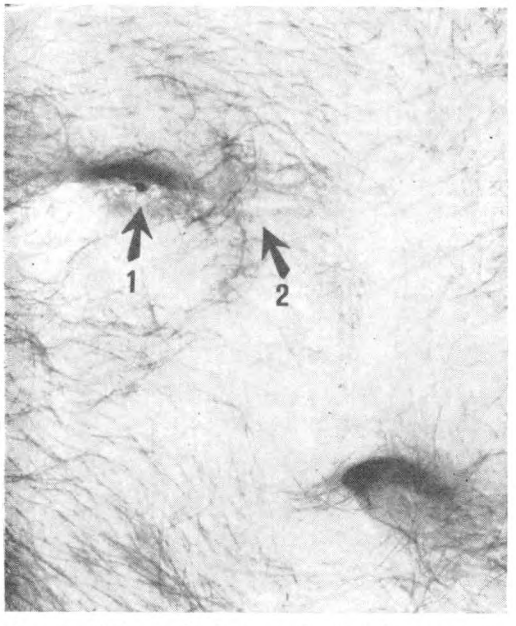


Fig. 1—Abdominal photograph. Fistulous opening in the right upper quadrant, Arrow 1; old operative scar, Arrow 2.

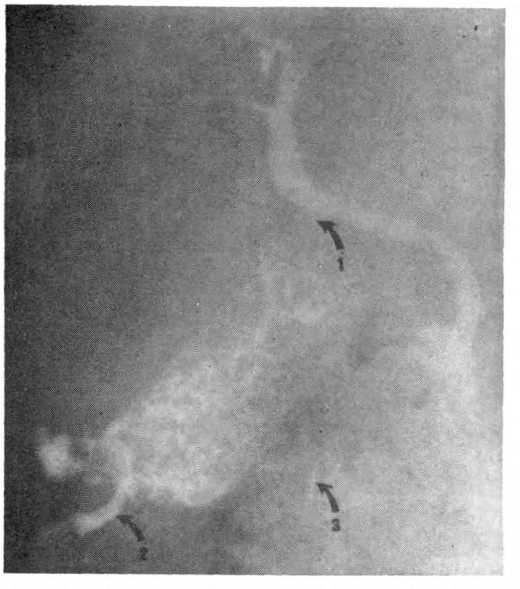


Fig. 2—Fistulogram demonstrating the cystic duct, Arrow 1; the skin fistula, Arrow 2 and suture material Arrow 3.

der was filled with small stones and adherent to the anterior abdominal wall via the fistula. The cystic duct was small and unobstructed. The gallbladder and sinus tract were removed intact (Fig. 3). A T-tube cholangiogram was normal. After an uneventful postoperative course, the patient was discharged.

Comment

Biliary fistula, secondary to gallstones perforating through the abdominal wall, was first reported by Thilesus in 1670.[4] In Europe, this entity is known as phlegmon of Jean-Louis Petit, who reported this complication of gallbladder disease in 1733.[5] Courvoisier in 1890 reported 499 cases of perforation of the gallbladder; of these 169 resulted in extension of the fistula through the abdominal wall.[6] Occasional cases are still reported in the European literature.[7-9] After 1900, the incidence of this complication greatly diminished and Henry and Orr collected only 36 cases in their review of the period from 1890 to 1948.[10] Fitchett found 20 cases reported in the world literature from 1948 to 1970.[3] Ruderman, in his review of the English literature described only 27 cases reported by 1975 and added four more of his own from Canada.[1]

Spontaneous external biliary fistulization occurs mainly in elderly women.[1-4] It is becoming so rare because the population with neglected gallstones is progressively being reduced. In these elderly patients, the serious nature of the problem may not be appreciated because of some degree of stoicism or cerebral atherosclerosis. In the present case, the patient was a younger man but because of his heroin use, he may have had little appreciation of pain or may have increased its use during times of discomfort.

Current evidence suggests that morphine is responsible for the pharmacologic effects of heroin and the action of morphine on the biliary tract is well



Fig. 3—Gross pathology of the gallbladder, probe is in the fistulous tract. Multiple stones were present.

known.[11] It causes a marked increase in common duct pressure along with spasm of the duodenum and sharp construction of the sphincter of Oddi. This spasm inhibits gallbladder emptying and causes a rise in intraductal pressure. Morphine has also been shown to decrease pancreatic and biliary secretions. In this case, these factors may have been operative in the formation of the calculi and subsequent rupture of the gallbladder.

Suppurative inflammation in the gallbladder in the presence of stones is the usual cause of spontaneous biliary abscesses and fistulas. Pericholecystitis accompanies cholecystitis and produces inflammatory adhesions between the gallbladder and adjacent structures. Ulceration extends through the wall of the gallbladder, perforating into adherent structures, forming a fistulous communication. External biliary fistulas usually involve the fundus of the gallbladder and present in the right subcostal area. Henry and Orr found that in a total of 206 cases, external perforation was in the right upper quadrant in 46.6%, the periumbilical region in 24.3%, the right lower quadrant in 15.0% and the region below the umbilicus in 7.3%.[10] This patient developed his fistula medial to an old operative scar. It is probable that local inflammation occurred after an episode of cholecystitis. The adhesions to the anterior abdominal wall from previous surgery served as an avenue for suppuration to the external abdominal wall with resulting perforation and discharge of the stones. If the cystic duct is obstructed by stone or inflammation, external perforation is hastened by increased pressure within the rupturing gallbladder. This patient's cystic duct was small and inflamed and the intraductal pressure may have been chronically increased by the heroin use.

The treatment of external biliary fistula is cholecystectomy with fistulectomy. In an elderly debilitated patient, treatment may be conservative and surgery deferred if the spontaneous drainage has been enough to release the abscess. The differential diagnosis should be made among subphrenic abscess with fistula, appendicitis with fecal fistula and hepatic or renal abscess with spontaneous fistulization. Discharge of gallstones through the fistula confirms the diagnosis and is impressive to the patient and physician. A fistulogram will outline the sinus tract and gallbladder.

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Clinical Vignette

The Transjugular Route as an Alternative to Direct Percutaneous Needle Biopsy of the Liver

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Transjugular liver biopsy was attempted in 32 cases of hepatocellular dysfunction with hemocoagulation disorders, ascites or marked obesity. A catheter was inserted in the right internal jugular vein and advanced into a hepatic vein under fluoroscopic control. A long needle was passed through the catheter and into the liver parenchyma for the biopsy. Diagnostic specimens were obtained in 28 instances (88%). The procedure was always well tolerated and no complications occurred. The transjugular approach offers a safe, practical alternative for liver biopsy in cases where direct percutaneous puncture is contraindicated.

Histologic examination of a tissue specimen has become indispensable in the modern diagnosis and therapeutic management of liver disease.[1, 2] Liver biopsy is easily achieved in most patients by means of the direct percutaneous needle technic. Danger from transperitoneal passage of the needle exists, however, for many patients, especially those with bleeding or clotting abnormalities. As performed through an indwelling hepatic vein catheter placed by standard angiographic technic, transvenous liver puncture does not violate the liver capsule and thus eliminates the potential complications of subcapsular hematoma, hemoperitoneum or bile peritonitis. Impressed by the results of Rösch, et al,[3] for the past two years we have investigated the use of transjugular liver biopsy in cases where transperitoneal liver puncture seemed contraindicated.

From the Departments of Radiology, Gastroenterology, Bridgeport Hospital.

Materials and Methods

Thirty-two patients with clinical and laboratory evidence of hepatocellular dysfunction had transjugular liver biopsies attempted at the Bridgeport Hospital from April, 1975 to September, 1977. None of the patients had known cancer or focal abnormalities on a radionuclide liver scan. None of the patients with jaundice had dilated biliary ducts demonstrated by ultrasonography. Indications for the transjugular approach were ascites (five cases), marked obesity (four cases), and coagulation abnormalities (23 patients).

As the biospy needle is rigid and straight, transvenous liver biopsy is easiest technically if the catheter is inserted from the right internal jugular vein rather than

TABLE I

SUMMARY OF HISTOLOGIC DIAGNOSES IN 32 CASES WITH ATTEMPTED TRANSJUGULAR LIVER BIOPSY

Liver biopsy diagnosis	Number of cases	Comment
Laennec's cirrhosis	10	1 patient not a known alcoholic.
Fatty liver	5	2 alcoholic patients; 2 obese patients.
Fatty liver and alcoholic hepatitis	1	
Primary biliary cirrhosis	1	65-year old woman with unexplained jaundice.
Hemosiderosis	1	75-year old man with hypersplenism.
Multiple granulomas	1	Patient improved on therapeutic trial of isoniazid.
Cholangitis	2	
Chronic active hepatitis	2	
Viral hepatitis	2	
Metastatic adenocarcinoma	1	
Normal liver	2	Patient No. 1: obese patient with abnormal liver tests which have returned to normal. Patient No. 2: sampling error. Clinically cirrhotic.
Fragmented tissue, inadequate for interpretation	3	
No tissue obtained	1	Unable to puncture jugular vein.

by the more aesthetically pleasing femoral or brachial routes.

Using a commercially available instrument set*, we employed the technic for transjugular liver biopsy described by Hanafee and Weiner.[4] After appropriate premedication and skin infiltration with a local anesthetic, a 9F Teflon catheter is inserted into the right internal jugular vein by the Seldinger technic. Under fluoroscopic control, the catheter is advanced through the right atrium and upper inferior vena cava and is wedged into a major hepatic vein. An 18-gauge modified Ross transseptal needle is passed through the catheter and with respiration suspended is thrust 1-2 cm. into the hepatic parenchyma. Fluoroscopic monitoring assures that the tip does not transgress the liver margin. Gentle aspiration during the thrusting maneuver retains the tissue specimen within the needle. The needle is withdrawn leaving the catheter remaining in the hepatic vein for additional needle passes if necessary. Multiple hepatic veins may be selectively catheterized and multiple biopsy specimens obtained. Hepatic wedge manometry and venography are performed if indicated.

Puncture of the right internal jugular vein causes apprehension for many physicians. This need not be so if a few anatomical references are kept in mind. The course of the needle should be parallel and about 1 cm. lateral to the course of the internal carotid artery. The angle of insertion of

* Cook Inc., Bloomington, IN.

the needle with the skin should be shallow (about 20°) to avoid inadvertent puncture of the deeper vertebral artery. The tip of the needle should be inserted through the skin at the level of the thyroid cartilage notch and should not pass caudally beyond the top of the clavicle to avoid the possibility of pneumothorax.

Results

A diagnostic biopsy specimen was obtained in 28 of the 32 cases (88%) (Table I). In one patient, the internal jugular vein could not be punctured; this occurred early in our experience. In 31 cases, liver tissue was obtained for histopathological analysis. In 24 cases, a long core of liver tissue was obtained averaging 7-13 mm. in length and 1-1.2 mm. in diameter. The biopsy specimen was fragmented in seven cases, three of which were interpreted by the pathologist as inadequate for tissue diagnosis. The reasons for fragmentation of the specimens were felt to be related to a hard, shrunken cirrhotic liver in five patients and inability to wedge the Teflon catheter firmly against the wall of a hepatic vein in two patients. Unless wedged, the biopsy needle tends to slide down the lumen of the vein.

No complications attributable to the transjugular liver biopsy were encountered in any of our cases. In one case after the biopsy specimen had been obtained, the patient experienced right upper quadrant pain and chills when we attempted to puncture the biliary system through the indwelling hepatic venous catheter. The symptoms disappeared quickly and there was no evidence of subsequent infection. The other 30 patients experienced only minor discomfort in the neck and abdomen. None of the 32 cases developed a hematoma in the neck.

Comment

We believe this series demonstrates that transjugular liver biopsy is a safe, well tolerated procedure with expectation of a high yield of diagnostic tissue samples. The diversity of diagnoses encountered in our study reconfirms the desirability of liver biopsy in patients with hepatocellular dysfunction.[1, 2] Transjugular liver biopsy offers a nonhazardous, practical alternative approach in cases with coagulation disorders, marked obesity or ascites, when direct transperitoneal biopsy is contraindicated.

The transjugular approach to the liver parenchyma was initially used for entrance into the biliary system for cholangiography.[5, 6] The safety and simplicity of the percutaneous "skinny needle" cholangiogram[7] has largely obviated the need for the more elaborate and less frequently successful transvascular method.[5, 8] We have attempted transjugular cholangiography after liver biopsy in many of our patients with presumably normal sized ducts and we still await our first successful study. Access to the portal vein and its tributaries is also possible via the transjugular route, although for most cases, direct percutaneous liver puncture is the preferred method of catheterization.[5]

Rösch, et al first investigated transjugular liver biopsy as an alternative to direct percutaneous puncture in 30 patients with bleeding disorders, marked hyperbilirubinemia (greater than 8 gm./100 ml.) or ascites.[3] They achieved diagnostic specimens in 27 instances without any complications except for a few minor hematomas in the neck. A recent paper[5] updates their experience to 83 cases. Many of the subsequent biopsies were obtained as a secondary procedure in conjunction with transjugular cholangiography. Presumably, these biopsies were not in high risk patients. In

any event, diagnostic specimens were obtained in 71 cases (86%) without a single major complication. Our results closely confirm these figures. In contrast, diagnostic samples are obtained by direct percutaneous biopsy in 93.2-98.8% of cases.[1]

Fragmentation of the tissue core accounted for procedure failure in three of four instances in our series, and in eight of 12 instances in Rösch, et al's 83 cases. Both groups employed the rigid, short bevelled, dull Ross needle as the biopsy instrument. Modifications of this needle would undoubtedly help resolve the problem of fragmentation. A more flexible end would make wedging against the wall of a hepatic vein easier. Retaining the blunt tip (to avoid perforating the catheter while passing the needle through it) but sharpening the rest of the cutting edge would facilitate puncture of a hard, cirrhotic liver. Modified needles have already been proposed.[8]

Addendum

Since the submission of the manuscript we have attempted 23 additional biopsies with six nondiagnostic studies. Two of these resulted from our inability to puncture the internal jugular vein. In four cases we were unable to wedge the biopsy needle in the parencyhma. No complications were encountered.

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Clinical Vignette

Jejunal Diverticulosis with Massive Hemorrhage

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A case of a relatively uncommon disease, jejunal diverticulosis, is reported. The case presented an unusual complication, massive melena. The patient was successfully treated and cured by resection of the involved portion of jejunum. In the management of gastrointestinal hemorrhage in the elderly one must always have in mind this infrequent pathological entity, especially when the small bowel is suspected as the site of bleeding.

The vast majority of lesions which cause gastrointestinal hemorrhage are located proximal to the ligament of Treitz and distal to the ileocecal valve. In contrast, bleeding from the mesenteric small bowel occurs infrequently, is difficult to diagnose and constitutes only 1.4% of all causes of gastrointestinal hemorrhage.[1]

One of the most unusual and extremely rare causes of massive small bowel bleeding is hemorrhage from jejunal diverticula. Uncomplicated jejunal diverticulosis is a very uncommon disease and has been reported to occur only in 1.3% of 300 routine autopsies performed by Rosedale and Lawrence.[2]

Although fewer than 40 cases of massive gastrointestinal hemorrhage from jejunal diverticula have been reported in the English language literature,[3] the small bowel should be considered as a potential source of bleeding in elderly patients presenting with massive melena or hematemesis.

We report a case in which jejunal diverticulosis presenting with massive bleeding was originally diagnosed ten years previously when the patient was 84 years of age. During hospital admission at that time the patient was managed conservatively with whole blood replacement therapy and recovered uneventfully. He then remained symptom-free and in excellent health until ten years later when he again presented with uncontrolled massive gastrointestinal bleeding.

Case Report

A 94-year old man, heretofore in good health, was admitted to Lenox Hill Hospital through the emergency room on the afternoon of 15 March 1977. He had passed large amounts of liquid and tarry stool in the last 48 hours. He complained of weakness and dizziness but was not in syncope. The patient, known to one of the authors (W.S.M.L.), was diagnosed as having jejunal diverticulosis following a barium swallow ten years prior to this admission. At that time he had been seen because of abdominal pain and indigestion (Fig. 1).

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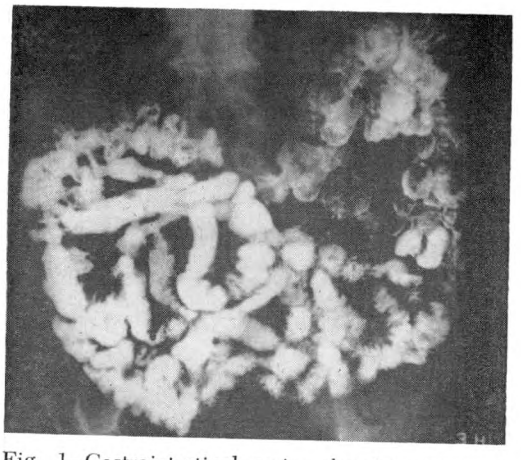


Fig. 1—Gastrointestinal series showing numerous diverticula, filled with barium, in the proximal portion of the jejunum.



Fig. 2—At operation large sized diverticula are seen bulging from the mesenteric portion of the jejunum.

Physical examination on this admission showed an apprehensive, weak, elderly man, markedly pale and showing signs of acute blood loss. The abdomen was slightly distended. No signs of peritonitis were detected. Bowel sounds were hyperactive. Hemoglobin was 6.1 gm.; hematocrit, 18.8%; white cell count, 12,000 with a slight shift to the left. He was stabilized by transfusion of four units of packed red cells and melena ceased almost completely. On the following day, as the patient's condition improved and his hemoglobin had risen to 11.2 gm., a mesenteric arteriogram was attempted to detect the source of bleeding. Because of extensive atherosclerosis the procedure was unsuccessful. On the third hospital day the patient suddenly passed several liquid bowel movements consisting of tarry, foul smelling stool. His condition deteriorated rapidly, progressing to a borderline shock condition and a laparotomy was performed. At operation multiple diverticula of the mesenteric border of the jejunum immediately distal to the ligament of Treitz were noted. These diverticula measured between 0.5 and 2.5 cm. in diameter (Fig. 2) and arose proximally from a level 15 cm. from the ligament of Treitz and extended distally to include a 70 cm. segment of jejunum (Fig. 3). After exclusion of the proximal bowel as a source of hemorrhage, blood was found in the aforementioned diseased segment. Careful inspection of the opening in the involved jejunum showed active arterial bleeding from one of the multiple large diverticula. Most of the other diverticula contained enteroliths and alimentary rests. A small bowel resection involving the portion affected by the diverticula was performed The patient's postoperative course was uneventful and there was no further bleeding or other sequels.

Comment

Diverticula arising in the small intestine are either congenital or acquired. The latter usually present as pulsion or false diverticula, herniating through the muscle layers in the mesenteric border in the small bowel.[4, 5] The vast majority of these diverticula are usually present in the proximal jejunum and are only rarely found in the ileum.[5, 6] Jejunal diverticulosis is an uncommon disease, afflicting more males than females in a ratio of 2:1.[3, 4] About 50% of the cases are associated with colonic diverticula[3] and there is an increasing incidence

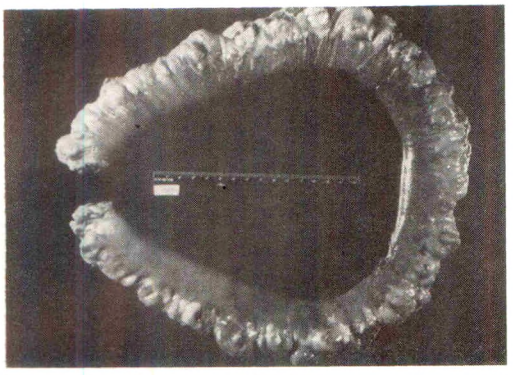


Fig. 3—Jejunal diverticula in the resected specimen.

of this condition in patients over 50 years of age. Complications occurred in 10.4% of 87 cases of jejunal diverticulosis in the Mayo Clinic over a nine-year period, as reported by Baskin and Mayo.[7] Massive hemorrhage from a bleeding jejunal diverticulum is a rare complication[3-5] and usually presents as a difficult diagnostic problem due to the site of this entity. In the English language literature, the first case of bleeding from jejunal diverticulosis was reported by Braithwaite in 1923.[8] Since then several authors have reported several cases.[9-15] Shackelford and Marcus, reviewing 24 cases of bleeding from jejunal diverticulosis,[6] pointed out that the usual clinical picture consists of anemia, massive or chronic melena with or without bloodless vomiting and or hematemesis, usually in an elderly person.

Once diagnosed, jejunal diverticula do not constitute an absolute indication for surgery.[14] They may be asymptomatic for years, as in our case. We must emphasize that one always should bear jejunal diverticulosis in mind as a possible cause of massive bleeding from the small intestine in the elderly.

The treatment of choice in such cases is complete resection of the involved segment and an end-to-end anastomosis.

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Clinical Vignette

Benign Mucocele of the Vermiform Appendix Secondary to Segmental Luminal Obliteration

Report of a Case

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A case is presented of benign mucocele of the tip of the appendix secondary to proximal luminal obliteration. This case offers further evidence that some cases of appendiceal mucocele are purely obstructive and not primarily neoplastic.

Introduction

A case of mucocele of the appendix secondary to obstructing endometriosis was recently reported.[1] After reviewing the theories regarding the etiology and pathogenesis of this uncommon condition, the authors concluded that the last word had not been written on this subject and that, despite the modern trend to consider appendiceal mucocele as basically neoplastic, it seemed "reasonable to assume that many cases will prove to have an obstructive etiology". We would like to record the following case as a clear-cut example of a purely obstructive mucocele.

Case Report

This overweight 19-year old girl, with a past history of urinary infections, presented with right lower quadrant pain of at least three days' duration. The pain was a constant ache, punctuated by occasional short-lasting colicky attacks and episodes of nausea and vomiting. There was no diarrhea or complaints referable to the genitourinary system. Clinically, palpation elicited pain at McBurney's point without rebound tenderness. Urinalysis and blood

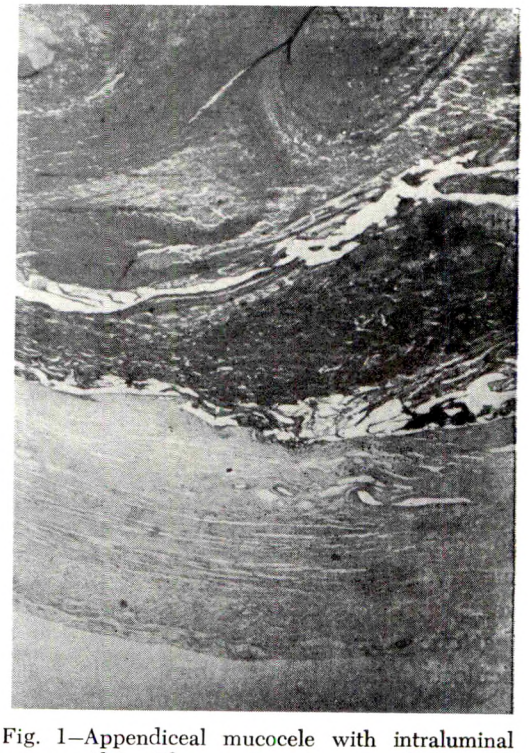


Fig. 1—Appendiceal mucocele with intraluminal Alcian-Blue positive mucus adherent to flattened submucosa. Note loss of epithelium, and absence of intramural tracking of mucus (PAS-Alcian Blue, original magnification x78).

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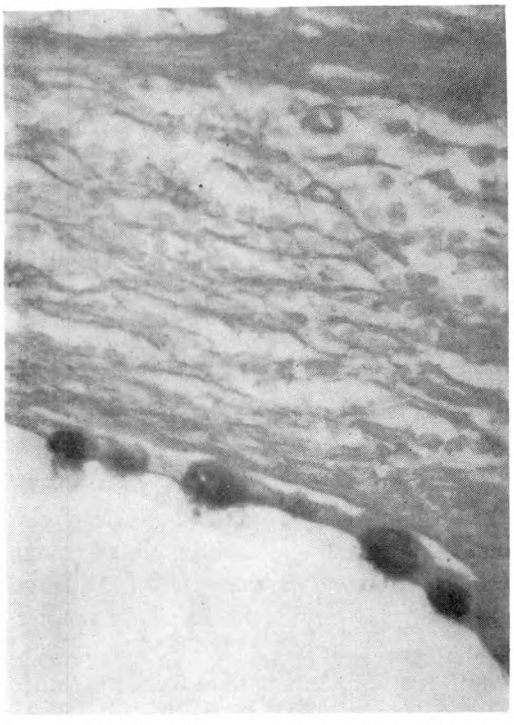


Fig. 2—Residual flattened appendiceal epithelium with Alcian-Blue positive goblet cells and compressed underlying lymphoid tissue (PAS-Alcian Blue, original magnification x78).

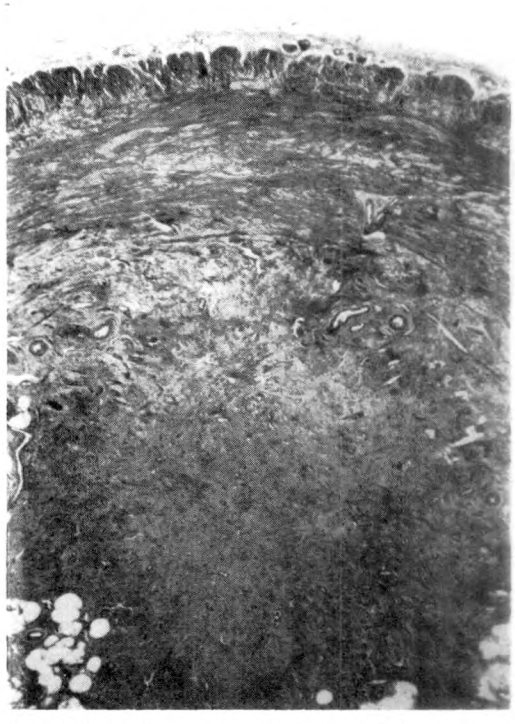


Fig. 3—Stenotic segment with loss of lumen and *lamina propria* and replacement by granulation tissue (Masson Trichrome, original magnification x52).

chemistry were normal and her hemogram showed no abnormality, not even a significant leucocytosis. The preoperative clinical diagnosis was appendicular colic and, at laparotomy, the only abnormality noted was distention of the tip of the appendix associated with stenosis of the proximal segment. The appendix was removed.

Pathologic Findings

Grossly the 6.5 cm. long appendix showed bulbous swelling of the tip with stenosis of the immediately proximal segment. On section, the distended tip, measuring 2 cm. in length and 8 mm. in diameter, was filled with sticky mucus under tension and its wall was 1-2 mm. thick. The stenosed segment, measuring 5 mm. in length and 3 mm. in diameter, had no detectable lumen and did not allow the passage of a probe. The proximal segment, 4 cm. long and 5 mm. wide, was grossly normal.

Histologically, the distended tip was filled with Alcian Blue-positive mucus (Fig. 1) and the epithelium was mostly absent with scattered persistent strips, lined by flattened cuboidal cells and occasional goblet cells (Fig. 2). The lymphoid elements and loose tissues of the submucosa were markedly reduced in amounts and the *muscularis propria* showed compression atrophy. No tracking of the mucus into the wall was seen to suggest incipient rupture or invasive colloid carcinoma. There was no acute inflammation in the wall.

The stenotic segment showed complete loss of epithelial glands and lymphoid tis-

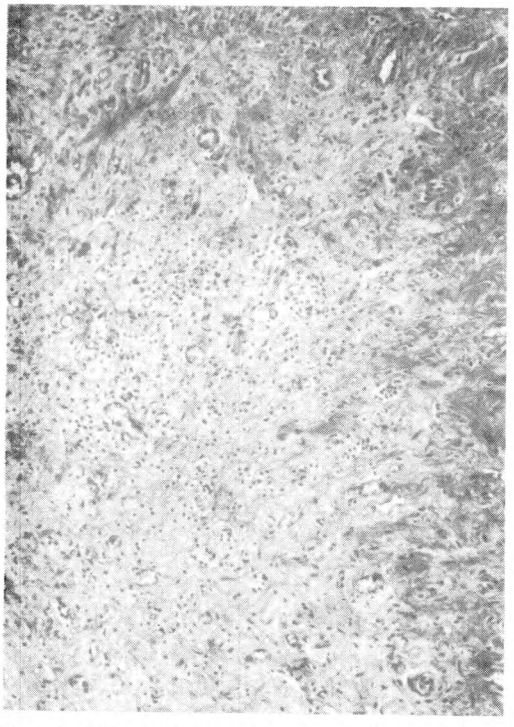


Fig. 4—Granulation tissue with patchy round cell infiltrate (Masson Trichrome, original magnification x328).

sue and replacement by active granulation tissue with a scanty round cell infiltrate (Figs. 3 and 4). The *muscularis* was intact and there was no serosal inflammation or fibrosis. The proximal segment was histologically normal with no inflammation, fibrosis, mucosal hyperplasia or neoplasia.

Comment

This case is a clear-cut example of a purely obstructive mucocele of the tip of the appendix. The mucocele itself was benign with subtotal loss of the epithelium and no evidence of mural invasion by carcinoma. The segmental stenosis, underlying the development of this mucocele, was due to luminal obliteration with replacement by active granulation tissue. No hyperplastic or neoplastic change was seen in the mucosa of the immediately adjacent proximal segment, which was grossly and microscopically normal.

Mucocele of the appendix is a well-recognized lesion with an incidence of 0.07-0.3% in surgically resected appendices.[2, 3] Its etiology and pathogenesis, however, still remain unsettled. Fraenkel[4] was the first to suggest that the mucocele was secondary to proximal luminal obliteration due to repeated attacks of mild appendicitis eventuating into mucosal loss and fibrous replacement. Experimental evidence was later provided for this concept.[5, 6]

In 1940 Woodruff and MacDonald[3] identified two groups of appendiceal mucoceles: one neoplastic and the other benign and obstructive, with marked preponderance of the latter. In 1968 Melcher and Ryan[7] further demonstrated the existence of two distinct types of mucocele: one obstructive and the other basically neoplastic. More recent reports[8-12] have tended to discount the existence of the obstructive mucocele and have stressed that this lesion is related to a primary neoplastic change in the appendiceal mucosa associated with excessive mucus production and secondary distension of the lumen. Obstruction, whether due to polyp formation, mucosal hyperplasia, or neoplasia plays only a secondary role.

The controversy has been reopened by the recent report of Hapke and Bigelow[1] of a purely obstructive appendiceal mucocele due to endometriosis. The marked discrepancy in the incidence of obstructive mucocele in the older and more recent reports raises the question as to whether this discrepancy is simply a reflection of a different conceptual attitude among pathologists or of a genuine change in the biology of the lesion. Is obstructive mucocele a real pathologic entity or is it a nonentity erroneously established before pathologists became

aware of its true nature, i.e. a distinctive lesion representing a spectrum of histologic changes ranging from mucosal polypoid hyperplasia through mucinous cystadenoma to mucinous cystadenocarcinoma?[12] Or is the change in incidence related to a marked increase in the occurrence of precancerous and cancerous lesions of the appendiceal mucosa associated with excessive mucus secretion and presenting as a mucocele? It is obvious that this controversy, with such important clinical implications, can only be solved by systematic investigation and reporting of all appendiceal mucoceles with full pathologic documentation.

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The Pediatric Corner

Recurrent Diarrhea in Older Children Associated with Enteropathogenic *E. Coli*

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Recurrent diarrhea associated with classic enteropathogenic *E. coli* serotypes developed in 31 older pediatric patients, four months to 13 years of age. Occult blood in the stools was present in five cases. Classic enteropathogenic *E. coli* most commonly 0127:B8 and 0111:B4, was found in stool cultures of all 31 cases. Appropriate antibiotic treatment eliminated the symptomatic pattern coincident with the eradication of the *E. coli* from the stool cultures. A brief summary of current concepts of causative mechanism and diagnostic methodology regarding enteropathogenicity of *E. coli* is presented.

Introduction

Various strains of *E. coli* are known to cause acute gastroenteritis in newborns and infants,[1, 2] although any age may be affected and increased susceptibility in infants less than six months of age has been a consistent feature.[3, 4] The onset may be insidious or abrupt. In older children, adolescents and adults, typical infection has been reported as a result of invasive *E. coli*, as well as noninvasive toxigenic strains (heat-stable).[5-7] Chronic or recurrent diarrhea has not been generally appreciated. This study reports on 31 older infants and children with recurrent diarrhea associated with enteropathogenic *E. coli*, discusses their clinical features (Table I) and the effect of treatment with antibiotics.

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Patients and Methods

Thirty-one children with enteropathogenic *E. coli* in stool, four months to 13 years of age, were identified from a total of 227 children with chronic diarrhea evaluated during a six-year period (1969-1974). Of these, 16 were over five years of age and four were less than two years of age; 19 were male, 12 female and of these, six were inpatients and 25 ambulatory. All were evaluated by the authors in a systematic manner.

Stools, a minimum of three at each study interval, were obtained in all initially and yearly thereafter; examined for reducing substances, occult blood by gram stain; cultured by standard bacteriologic methods, including enrichment broth and examined for ova and parasites. Direct plating was performed on eosin-methylene blue agar, Salmonella-Shigella agar and on sheep red blood cell agar.

Suspicious lactose-fermenting colonies were subcultured, and random isolates with biochemical reactions of *E. coli* underwent determination of serotype and somatic O, surface K(B) and Flagellar H antigens.[3, 4, 6] Sensitivity tests on the microorganisms were performed using the antibiotic disc diffusion method on nutrient agar. Due to the timing of this study, assays for heat-labile and heat-stable enterotoxin production were available for only three cases (01277:B8, 2, and 055:B51) and were performed using procedures adapted from Gorbach, et al[5] and Ryder, et al.[7] Enteroin-

TABLE I

SUMMARY OF CLINICAL FEATURES

	No.	%
Diarrhea (31)		
Every 4-7 days	9	29.0
Every 1-4 weeks	14	45.2
Every 1-4 months	8	25.8
Each episode: 4-7 days	14	45.2
Each episode: 1-4 weeks	16	51.6
Each episode: 1-3 months	1	3.2
Total duration: 3-6 months	7	22.6
Total duration: 6-12 months	12	38.7
Total duration: 1-5 years	12	38.7
Blood in stools (microscopic)	5	16.1
Fever	1	3.2
Weight loss (less than .9 kg.)	2	6.5
Anorexia	1	3.2

vasiveness was also tested on only these three cases using the procedure adapted from Rudoy, et al.[8]

A complete blood count, urinalysis, sedimentation rate, serum electrolytes, and blood urea nitrogen were obtained on all patients. Proctoscopy and rectal biopsy were performed in nine patients.

RESULTS

Clinical features (Table I):—Recurrent diarrhea, consisting of at least four loose or watery stools per day, was observed in all patients. The pattern of recurrence is listed in Table I. In five patients the stools were positive for occult blood on more than one occasion. No patient had gross hematochezia or melena. Other symptomatology included fever in one patient, weight loss (less than .9 kg.) in two and anorexia in one. Physical examination was unremarkable in all patients. Pathogenic *E. coli* were cultured from the stools of these 31 children. The isolated strains are shown in Table II. Antibiotic disc diffusion studies revealed sensitivity to neomycin in 29 patients to colymycin in 31 and to others, e.g., ampicillin in 22. All stools were negative for ova and parasites and reducing substances.

TABLE II

ISOLATED (*E. coli*) FROM STOOL

Type	Number (Age-related)		
	4 mo.-2 yr.	2-5 yr.	5-13 yr.
0127:B8		4	7
0111:B4		5	3
0126:B16	3		2
0126:B12	1		
055:B5		2	
026:B6			1
0119:B14			1

The three assays for heat-stable and heat-labile enterotoxin were negative. The three tests for invasiveness were negative, too.

Complete blood counts revealed normal hemoglobin and hemotocrit levels in 30 patients and low level in one (10.0 gm./100 ml., 31% respectively); white blood count, 4,600-11,700/cu. mm. (mean: 7,800/cu. mm.), with a normal differential count in all patients. The sedimentation rate, serum electrolytes and blood urea nitrogen were unremarkable in all patients.

TREATMENT

Treatment with neomycin in 26 patients and colymycin in five eliminated the diarrhea after five to 13 days (mean 8.3 days). Repeat stool cultures, a minimum of three at each study interval, were negative for pathogenic *E. coli* in all patients. No known recurrences (symptomatology,

culture) have occurred during follow-up of one to five years (mean 3.1 years).

Comment

The association of *E. coli* and diarrhea in infants was observed as early as 1923.[1] In 1947, the Kauffmann classification allowed specific serotyping and thereby the delineation of enteropathogenic strains.[8] During recent years properties of strains of *E. coli* have been clarified and two mechanisms of enteropathogenicity (diarrhea) have been defined as enterotoxin production and mucosal invasion.[5-7] Strains of *E. coli,* nonenteropathogenic by serotpying, have been isolated from patients with diarrhea and have produced heat-stable or heat-labile enterotoxin, or both.[5-7] This enterotoxin production is apparently plasmid mediated, while the antigenic determinants of invasive *E. coli* are mediated chromosomally.[6, 7] Yet, some classic enteropathogenic serotypes which produce diarrhea, do so not by either of the two proposed mechanisms of enteropathogenicity and are seldom present in normals.[9, 10]

The usual clinical pattern of enteropathogenic *E. coli* is that of an acute diarrheal syndrome, variable in severity. With the severe form, stools are frequent and may contain blood and white blood cells. Tenesmus, fever and vomiting may also be present.[6, 10]

Chronic diarrhea in pediatric patients has not been appreciated to any extent. In particular, recurrent diarrhea, *per se*, has been a rarity, especially in older infants and children. This report has documented 31 older patients with recurrent diarrhea, without other significant symptomatology, associated with classic enteropathogenic *E. coli* serotypes and their apparent causative relationship suggested by confirming the elimination of the symptomatic pattern, coinciding with the eradication of the *E. coli* from stool cultures after appropriate antibiotic treatment. Thus, stool cultures with classical serotyping should be considered in the evaluation of such patients, as well as examination for enterotoxin production and mucosal invasiveness.

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State of the Art*

Therapeutic Strategies in Crohn's Disease

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One's therapeutic stance regarding the treatment of Crohn's disease ought, I suppose, to bear some relation to one's concept of the disease. As an article of faith, I believe Crohn's disease is an inflammation occurring anywhere along the gastrointestinal tract but more intensely behind sphincters, due to an as yet unidentified microbiological agent in a susceptible population with some as yet incompletely characterized immunological defect. But unfortunately I cannot relate present day therapeutic management to this concept.

We move here in the realm of the empiric. All therapy is palliative, none is curative. My conviction, based on a good sized sample, is that the disease will inevitably recur no matter what our therapies but we must focus more on the quality of life between recurrences whether "induced" or "spontaneous".

The management of some complications of Crohn's disease offer little room for controversy. True perforation and uncontrollable massive hemorrhage obviously require prompt surgical intervention. While elemental (nonresidual) diets may be used to manage patients with increasing stenotic lesions for temporary periods of time, they simply delay the period of surgical intervention. This delay, however, may be useful in attempting to assess the contributions of fixed stenosis, functional spasm and acute inflammatory changes to the obstructive symptoms.

An abscess is an abscess no matter where or when it occurs, in the abdomen or in the perineum and perianal area and requires incision and drainage. Antibiotics directed against intestinal anaerobes and aerobic inhabitants are purely adjunctive. These last statements do not deny the fact that at times it may be very difficult to decide whether a tender swelling in the abdomen is indeed an abscess or a matted inflamed omental and/or intestinal mass. Unfortunately sonography has not helped as much as one would have hoped for and gallium scanning has proven definitely misleading.

Abdominal cutaneous fistulas may close spontaneously, may fluctuate with the degree of activity of the underlying intestinal disease and may even respond to our drugs but the majority in my experience will require a surgical attack. Even if they close under total parenteral nutrition, they invariably recur when feeding by mouth is resumed. I have some good luck in the closure of perianal fistulas with azathioprine but not enough. Control of the underlying disease substance is the central factor. Even in the absence of significant colonic or anal disease I have been reluctant to advise fistulectomy in these patients, perhaps not appreciating the advances that surgeons have made in this area of operation.

If I cannot manage the patient satisfactorily under realistic life situations and conditions, then the decision as to surgical removal of diseased tissue must depend on whether a reasonable amount of functional small bowel can be left behind. Absorptive

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tests of small bowel function may help in this decision but they are weak reeds to lean on. When the decision to intervene has been made, removal of as much grossly diseased tissue as possible is in order. An experienced surgeon's gross judgment is no less reliable than frozen sections done of the resected portions of intestine. Except when an unexpected abscess or the possibility of injury to the ureter prevents this, by-pass operation, with or without exclusion, should be avoided. The danger of the development of cancer in these by-passed loops is clearly now beyond the realm of chance. In patients who have had by-passes years ago, I am using every opportunity I can to excise these by-pass areas. It should also be remembered, in this context, that a by-passed loop may on rare occasions reactivate and be the site of trouble.

While anastomosis in Crohn's disease clearly increases the risk of recurrence, yet common sense dictates that this will always be done in small bowel disease and should be done, if at all feasible, in colonic disease. An ileoproctostomy may be feasible in some instances of Crohn's colitis but recurrence in the rectal segments seems to occur more promptly than one expects or hopes.

With the recognition that Crohn's rather than ulcerative colitis is the chief inflammatory bowel disease associated with amyloidosis, one ought to look for this more frequently and especially in patients with proteinemia. Excision of Crohn's colitis has led to remission of hepatic and renal amyloid in documented cases.

And finally, to put in proper perspective this section on my approach to surgical intervention, one ought always to balance the destructive effects of chronic invalidism, the adverse physical and psychological effect of current steroid therapy, the unknown long-term effect of immunosuppressive therapy in these often young patients not only against the rate of recurrence but more importantly against the quality of life between operations.

Medical Management

My goals in medical management are modest: to relieve the patient's symptoms and to support him in the hope that he will go into a shorter or longer remission, on the assumption that any maneuver which increases the patient's "resistance" is worthwhile. So we are concerned with management of the patient as a totality and all the old clichés hold.

Since the laws of thermodynamics will not be defied, the balance between energy input and energy output should be scrutinized. There is no evidence that diet causes or cures Crohn's disease. Lactose intolerance is rare and patients have only discovered this tolerance for milk and milk products long before they consult me. Their experience is a much more valuable procedure than a formal lactose tolerance test. In the presence of active diarrhea or stenotic lesions, it is reasonable to reduce the fiber content of the diet but in their absence it makes little sense to arbitrarily reduce dietary residues. These patients suffer enough from arbitrary restriction in food intake composed of folklore and iatrogenic suggestions. The anorexia of fever and pain however, clearly limit appetite.

It is obvious that I have postponed drug therapy to the last, since we have so little that is specific. In patients well enough to be treated with an ambulatory program Azulfidine® is my first line choice. I believe it is better to start with low dosage levels and build up slowly. Some intolerance can be managed by the enteric coated form but not much. To those truly intolerant I fall back on the group of nonabsorbable sulfonamides we used before the introduc-

tion of Azulfidine: sulfathaladine and sulfasuxadine. I try to avoid steroids and especially long-term steroids but frequently use them out of desperation. In patients sick enough to be hospitalized I have no rationale to choose between ACTH and hydrocortisone for the parenteral use of steroids, except perhaps the patient's previous history. Far from an enthusiast for immunosuppressive therapy, I reserve azathioprine or 6 mercaptopurine for extensive nonresectable disease or in an effort to reduce the dose of oral steroids. When colonic bacterial overgrowth secondary to stricture or intestinal anastamotic operations is present, a trial of tetracycline is justified and at times useful. While the use of a variety of antibiotics is currently being tried in the "underground" therapy of Crohn's disease, including ampicillin, gantrisin, humatin (paromycin), there is no justification in published experience. They only represent our desperation. Flagyl (metronidazole) in the toxic doses recommended frightens me. Cromolyn and levamisole remain purely experimental.

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The Radiology Corner*

Pseudopolyposis as the Only Manifestation of Ulcerative Colitis

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Introduction

Diffuse pseudopolyposis may present as the only radiographic manifestation of quiescent ulcerative colitis. Without evidence of previous or current inflammatory disease pseudopolyposis can be a diagnostic problem. This problem is magnified if the pseudopolyposis is restricted to only a segment in an otherwise normal appearing colon.[1-3]

Case Report

A 44-year old male presented four years previously with an acute episode of toxic megacolon. A diagnosis of ulcerative colitis was presumed and the patient placed on steroids which resulted in complete remission within three months. Barium enema examination, performed six months after admission, showed multiple polypoid filling defects involving the distal transverse, descending and sigmoid colon. No other radiographic evidence of ulcerative colitis was seen (Fig. 1).

The patient remained without treatment or symptoms for four years. He then returned with a two-week history of painless bright red rectal bleeding. A barium enema at this time showed multiple diffuse polypoid projections in the exact location as previously described. The masses appeared somewhat larger and more irregular than on the previous examination. No evidence of inflammatory disease was identified (Fig. 2).

The patient underwent colonoscopy to the ileocecal valve. Findings consisted of pseudopolyposis that extended from the sigmoid colon to beyond the splenic flexure. The colonic mucosa appeared normal except in the region of the pseudopolyposis where it was noted to be inflamed, friable and edematous. Biopsies were taken and read as severe acute colitis compatible with ulcerative colitis. The patient was started on treatment with Azulfidine and he was in complete remission at the time of discharge.

Comment

In most cases of pseudopolyposis associated with ulcerative colitis, evidence of an inflammatory process is apparent, with absence or irregularity of haustral markings, narrowing of the lumen, longitudinal shortening of the colon or ulceration of the mucosa.[4] Those cases in which the inflammatory process heals and the surrounding radiographic changes return to normal can have been confused with: 1. familial polyposis; 2. granulomatous colitis; 3. lymphosarcoma; 4. amebic colitis.

* Edited by Richard H. Marshak, M.D., F.A.C.G. and Arthur E. Lindner, M.D., F.A.C.G.

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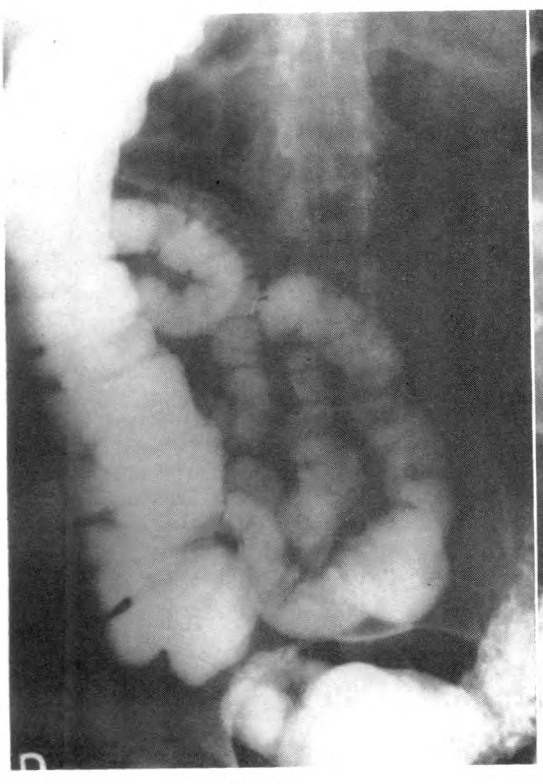


Fig. 1



Fig. 2

Fig. 1—Initial barium colon examination demonstrating diffuse pseudopolyposis involving the left colon. Patient was asymptomatic at this time.

Fig. 2—Barium colon examination done four years later again shows marked pseudopolyposis involving the distal transverse, descending and sigmoid colon. No other roentgenologic evidence of ulcerative colitis is demonstrated.

An adequate history and a proper clinical evaluation are of utmost importance in obtaining the correct diagnosis.

Distinguishing ulcerative colitis from familial polyposis on the basis of the polyps themselves may be impossible.[5] The radiographic similarity in appearance and distribution of these lesions has been widely reported. Except for those cases of ulcerative colitis with pseudopolyposis and backwash ileitis (familial polyposis rarely involves the small bowel), differentation must depend on clinical history and tissue biopsy.

The nodular thickening of the mucosa and submucosa associated with granulomatous colitis rarely produces an appearance similar to that of multiple polyps. Usually the postevacuation film is sufficient to demonstrate the cobblestone pattern produced by longitudinal and transverse ulcerations. Other findings of granulomatous colitis generally present are: skip lesions, narrowing, frequent fistulas or abscesses and irregular shortening. Recently, several cases of localized giant pseudopolyps associated with granulomatous colitis have been reported.[6]

Lymphosarcoma with sole involvement of the colon is rare.[7] It also presents in two forms, diffuse and localized. The roentgen features of diffuse lymphosarcoma consist of exaggeration of the mucosal fold pattern

combined with innumerable sessile polypoid protrusions into the lumen. In severe cases, the barium enema shows transformation of the mucosal pattern into an irregular cobblestone appearance with coarse folds and finger-like projections into the lumen. These rare cases are very difficult to differentiate from the mucosal destruction and pseudopolypoid projections of ulcerative colitis.

There are several reports in the literature of patients with amebic colitis presenting with a radiographic and clinical picture nearly indistinguishable from ulcerative or granulomatous colitis.[9] Colonic pseudopolyps, however, are still considered an exceedingly rare manifestation of this disease. When present, it is radiographically indistinguishable from pseudopolyposis presenting as the only indication of inflammatory bowel disease.

This case was chosen for its unusual presentation of pseudopolyposis as the only radiologic manifestation of the disease process. The radiographic picture remained relatively unchanged for four years, although some enlargement and increased irregularity of the pseudopolyps secondary to acute inflammation and edema did occur. This picture alone would have raised the question of other possible etiologies if previous history had not been available.

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EDITORIAL

Valedictory

The old order changeth, making way for the new—so with this issue I step aside as Editor-in-Chief of the Journal. Having served the traditional two terms, I transfer with pleasure the responsibility to my friend and Associate Editor, Arthur E. Lindner, M.D., F.A.C.G. In his capable hands, rest assured the Journal will flourish.

Long association with the Journal makes it difficult for me to just fade away. Dr. Lindner has agreed that I continue editing foreign papers and reviewing medical texts. I am delighted so to do.

I could not say goodbye without expressing my thanks to Mr. Daniel Weiss for the tremendous assistance he has given me throughout my tenure. My appreciation is also due to the Editorial Board, the Associate Editors and the panel of reviewers who have so ably assisted me in my tasks and responsibilities.

With this issue comes the first change in the staff of the publication. *The Last Page*, which has been a feature of the Journal and was edited by Michael Ruoff, M.D., F.A.C.G. is now being prepared by Charles G. Hazzi, M.D., F.A.C.P., F.A.C.G.

Dr. Ruoff will be the new Associate Editor. My sincere thanks to him and the excellent work he has done in the past and I wish both Dr. Ruoff and Dr. Hazzi well in their new positions.

David A. Dreiling, M.D., F.A.C.G.

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The Last Page

Questions in Gastroenterology

CHARLES G. HAZZI, M.D., F.A.C.P., F.A.C.G.*
New York, N. Y.

The Last Page appears as a regular feature in each issue of The American Journal of Gastroenterology.

The questions that follow have been prepared exclusively from material in the current issue of the Journal and the page on which the answer can be found is indicated with each question.

One way for regular readers of the Journal to utilize this feature is to scan *The Last Page* and attempt to answer the questions before reading the Journal. Then, when the articles have been read, return to *The Last Page*, again try to answer the questions and finally refer to the page locations that are provided in order to confirm your answers.

For each question, one or more responses may be correct, or none may be correct.

1. GASTRIC EMPTYING, ATROPINE AND GLUCAGON:

   A. Both drugs slow gastric emptying.

   B. This effect is unrelated to depression of antral peristalsis.

   C. Only atropine decreases total gastric acid secretion.

   D. Glucagon raises blood sugar, while atropine lowers it.

   (Page 581)

2. GASTRIC AND DUODENAL LESIONS FOLLOWING ALCOHOL INGESTION:

   A. Are diffuse and may be diagnosed by blind biopsy.

   B. Are least marked near the pylorus and do not extend beyond the bulb.

   C. Appear histologically as subepithelial hemorrhage with an eosinophilic infiltrate in the duodenum.

   D. May follow a single dose of alcohol in man.

   (Page 587)

3. WITH CHOLECYSTOKININ CHOLECYSTOGRAPHY:

   A. Abnormalities will be found in all patients with biliary pain and normal oral cholecystogram.

   B. A positive response consists of reproduction of pain and abnormal radiographic responses.

   C. Both hypercontraction and absence of contraction of the gallbladder are abnormal.

   D. A dilated common bile duct measures more than 7 mm.

   (Page 593)

4. SUBACUTE HEPATIC NECROSIS (BRIDGING) ON LIVER BIOPSY IN ACUTE HEPATITIS:

   A. Is more serious in HBsAg negative hepatitis.

   B. Has a graver prognosis in the younger patient.

   C. Is associated with a 10% mortality.

   D. Frequently progresses to cirrhosis.

   (Page 600)

* Assistant Professor of Clinical Medicine, New York University School of Medicine.

5. VENO-OCCLUSIVE DISEASE OF THE LIVER:

   A. Is due to ingestion of certain pyrrolizidine alkaloids.

   B. Presents clinically as a fulminant illness with deep jaundice and minimal ascites formation.

   C. Occurs when the vascular flow in the sinusoids is blocked following primary injury to the hepatocytes and sinusoidal epithelium.

   D. Can be identified pathologically in humans by the presence of megalocytosis.

   (Pages 607 and 608)

6. CONCERNING SCLEROSING CHOLANGITIS:

   A. Ulcerative colitis is the commonest disease associated with it.

   B. The diagnosis can be made in the presence of gallstones or malignancy.

   C. Liver biopsy reveals bile duct proliferation, portal inflammation, fibrosis and bile plugs.

   D. Total colectomy will always arrest the disease in ulcerative colitis.

   (Page 614)

7. ANGIOGRAPHY OF THE PANCREAS MAY SHOW:

   A. Fifty per cent false positive findings in the absence of pancreatitis or carcinoma.

   B. Serpiginous or serrated encasement or occlusion of arteries as frequently in chronic pancreatitis as in carcinoma.

   C. High incidence of involvement of extrapancreatic arteries in carcinoma.

   D. Abnormalities of capillary phase only with pancreatic disease.

   (Page 620)

8. PANCREAS-PAROTID GLAND INTERACTION IS DEMONSTRATED BY:

   A. Abnormal salivary secretion in the patient with pancreatic disease and animals with experimental pancreatitis.

   B. Secretin, CCK-PZ and pentagastrin augmenting flow, bicarbonate and enzyme output of both pancreas and parotid.

   C. A probable neurogenic mechanism in the rat linking experimental pancreatitis and parotid gland impairment.

   (Pages 627 and 635)

9. IN ACUTE PANCREATITIS THE PRODUCTION OF KALLIKREIN:

   A. Is increased, especially in patients with hypotension.

   B. Correlates directly with inflammatory indices.

   C. Reduces pain by blocking afferent nerve endings.

   D. Increases the permeability of the capillaries and induces edema formation.

   (Page 645)

10. SPONTANEOUS EXTERNAL CUTANEOUS BILIARY FISTULA:

   A. Is more common now than prior to 1900.

   B. Occurs mainly in elderly women.

   C. Morphine may predispose to it by contracting the sphincter of Oddi.

   D. Treatment should be conservative.

   (Page 649)

11. TRANSJUGULAR NEEDLE BIOPSY OF THE LIVER:

   A. Is useful when clotting abnomalities, ascites or marked obesity contraindicate direct biopsy.

   B. Does not reduce the risk of subcapsular hematoma, hemoperitoneum or bile peritonitis.

   C. Allows multiple biopsy specimens to be obtained.

   D. Permits measuring hepatic vein pressures and hepatic venography if indicated.

   (Page 653)

12. BLEEDING JEJUNAL DIVERTICULOSIS:

   A. The small bowel is a frequent source of gastrointestinal hemorrhage.

   B. Less than 40 cases of massive bleeding from jejunal diverticula have been reported reported in the English language literature.

C. Diverticula of the ileum are more common than in the jejunum.

D. Small bowel diverticula are often associated with colonic diverticulosis.

(Page 657)

13. MUCOCELE OF THE APPENDIX:

A. Has an incidence of 0.07-0.3% in surgically resected appendices.

B. Is basically a neoplastic lesion and not due to benign proximal obstruction.

C. The tumor may be a mucinous cystadenoma or cystadenocarcinoma.

(Page 660)

14. CONCERNING ENTEROPATHOGENIC *E. COLI*:

A. Never cause chronic or recurrent diarrhea.

B. Either enterotoxin production or invasiveness can always be demonstrated.

C. Are usually sensitive to neomycin, colimycin or ampicillin.

D. The most common serotypes are 0127:B8 and 0111:B4.

(Page 664)

15. IN CROHN'S DISEASE:

A. There is no increased risk of developing cancer in surgically by-passed loops of bowel.

B. The risk of amyloidosis is greater than in ulcerative colitis.

C. Azathioprine may be used in an effort to reduce the dose of steroids.

(Page 667)

16. PSEUDOPOLYPOSIS IN ULCERATIVE COLITIS:

A. Disappears when colitis is in remission.

B. May be confused with familial polyposis, granulomatous colitis, or lymphosarcoma.

C. Is as common as in amebic colitis.

(Page 670)

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NEWS NOTES

Current Concepts in Gastrointestinal Disease

The American Gastroenterological Association Postgraduate Course, Current Concepts in Gastrointestinal Disease will be held on 19, 20 May 1979, in the Rivergate Convention Center, New Orleans, LA. The Course Director is Robert M. Glickman.

The first day of the course will be a discussion concerned with current concepts of the physiology and pathophysiology of the small intestine. Following the formal presentations, two hours will be devoted to smaller group discussions with approximately 140 registrants and two faculty members.

During the second day of the course, the registrants will be divided into two groups of approximately 900 each. Each group will have the opportunity to select in either the morning or afternoon session two 1½ hour Seminars in Gastroenterology from a list of 13 topics (approximately 70 registrants per seminar group). In addition each group of 900 registrants will be exposed in either the morning or afternoon session to a series of Brief Updates of Important GI Topics with an opportunity for discussion.

Registration will be limited to 1,800 persons.

Further information may be obtained by writing to: Sally Grasso, Charles B. Slack, Inc., 6900 Grove Road, Thorofare, NJ 08086.

Endoscopy 1979

The Eighth Annual National Postgraduate Course, Endoscopy 1979, will be given by the American Society for Gastrointestinal Endoscopy during Digestive Disease Week on Thursday and Friday, 24, 25 May 1979, in New Orleans, LA. The one and a half day course will emphasize some of the newer endoscopic technics in upper gastrointestinal endoscopy, colonoscopy, ERCP and laparoscopy. The format will include lectures, panel discussions and small group seminars. A distinguished faculty has been assembled from the United States and Europe to present the Course.

The Course Director is John F. Morrissey, M.D. For further information contact Sally Grasso, A/S/G/E Postgraduate Course Coordinator, Charles B. Slack, Inc., 6900 Grove Road, Thorofare, NJ 08086.

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BOOK REVIEWS FOR GASTROENTEROLOGISTS

The Sphincter of Oddi. Proceedings of the 3rd Gastroenterological Symposium: edited by J. Delmont. 259 pages, illustrated. S. Karger AG, Basel, Switzerland, 1977. Price $30.00.

The Sphincter of Oddi is a pesky valve which has bedeviled the physiologists for years. This report of a symposium in 1977, tells you all which is known, as well as all which is unknown concerning its structure, function and roles in human digestion as well as in the etiopathogenesis of pancreatico-biliary disorders.

DAVID A. DREILING, M.D., F.A.C.G.

Surgical Techniques Illustrated, Vol. 2, No. 4, Surgery for Chronic Pancreatitis: edited by Ronald A. Malt, M.D. 102 pages, illustrated. Little, Brown and Company, Boston, MA, 1977. Price $68.00 per yr.

I liked this one. Why? Because of my interest in pancreatic surgery. Granting my sophistication in this area, you should accept my opinion that this surgical atlas of operations for chronic pancreatitis is superb. A good test for a surgical departmental library.

DAVID A. DREILING, M.D., F.A.C.G.

Glucagon: Its Role in Physiology and Clinical Medicine: edited by Piero P. Foa, M.D., Jasbir S. Bajaj, M.D. and Naomi L. Foa. 793 pages, illustrated. Springer-Verlag New York Inc., New York, NY, 1977. Price $24.80.

Edited by Piero P. Foa, a pioneer in glucagon research, this text presents topics selected from a special symposium dealing with the subject, glucagon. This symposium followed the IX Congress of the International Diabetes Federation.

Although glucagon secretion, mode of action and metabolic and physiologic effects are dealt with, little is said about the motor effects of glucagon.

This book belongs in every medical school library and should be available for teachers and clinicians interested in endocrinology and metabolism. It is a bargain at the purchase price.

WALTER HARVEY JACOBS, M.D., F.A.C.G.

Diagnosis of Liver Diseases: edited by H. Wallnofer, M.D., Ed Schmidt, M.D. and F. W. Schmidt, M.D. 298 pages, illustrated. Stratton Intercontinental Medical Book Corporation, New York, NY, 1977. Price $65.00.

The text on Liver Diseases is a very condensed illustrated atlas combining the ingredients which lead to diagnosis. After two preliminary chapters devoted to anatomy, physiology and biochemistry of the norm as well as nonclinical deviations, the infectious, reactive, nutrition, toxic, oncology and functional diseases of the liver are presented with their characteristic alterations in: 1. liver function tests; 2. scintigraphy; 3. sonography; 4. angiography; 5. laparoscopy; 6. gross pathology (needle biopsy); 7. electron microscopy.

A very well executed textbook.

DAVID A. DREILING, M.D., F.A.C.G.

Alvarez on Alvarez: by Walter Clement Alvarez, M.D. 152 pages, illustrated. Strawberry Hill Press, San Francisco, CA, 1977. Price $5.95.

The fly leaf reads "A humanitarian, a scholar, a healer of bodies and minds, the best known popular medical writer in the world today—a gentle and loving man ninety-three years young—reminisces about his life." It is true.

Practitioners of medicine can learn much from the life of this ninety-three year old, alert "great man of medicine".

Hesse said, in Siddhartha, "Knowledge is not wisdom". We can learn from the wisdom expressed here.

I would suggest this book for all hospital and medical libraries and for all students of the art of practicing medicine.

WALTER HARVEY JACOBS, M.D., F.A.C.G.

Current Views in Gastroenterology, Vol. 1: edited by V. Varro, M.D. and G. A. Balint, M.D. 724 pages, illustrated. Kultura, Budapest, Hungary, 1977. Price $38.00.

This is a well edited text of the Proceedings of the Symposia and Round Table Conferences of the 10th International Congress of Gastroenterology held in Budapest in 1976. While the papers are excellent, the material is over two years old and, therefore, of interest probably only to the participants.

DAVID A. DREILING, M.D., F.A.C.G.

Computed Tomography of Abdominal Abnormalities: by John Haaga, M.D. and Norbert E. Reich, D.O. 430 pages, illustrated. The C. V. Mosby Company, St. Louis, MO, 1978. Price $44.50.

This is another one of those excellent heavy texts on C.A.T. The authors have limited their presentation to the abdomen and have been a magnificent job. I carefully went through the chapter on pancreas since this is an area of my expertise. It is beautifully illustrated and highly informative. Worth owning.

DAVID A. DREILING, M.D., F.A.C.G.

Operative Surgery Series, Abdomen, 3rd edition: edited by Hugh Dudley, M.D., Charles Rob, M.D. and Sir Rodney Smith. 509 pages, illustrated. Butterworths, Woburn, MA, 1978. Price $95.00.

Rob and Smith's 3rd edition of Operative Surgery is even more lush than the previous. This is an absolute must for the general and surgical libraries of medical schools and teaching hospitals. Not only are abdominal procedures beautifully illustrated but the accompanying text, though terse, is always useful. The general surgical resident can profit much from a cover to cover perusal. The medical and gastroenterology resident could likewise benefit in more than a cultural fashion. It might give them greater insight into the perils and problems confronting the surgeon.

DAVID A. DREILING, M.D., F.A.C.G.

International Histological Classification of Tumours: No. 15: Histological Typing of Intestinal Tumours: by B. C. Morson, M.D., F.A.C.G. (Hon.), L. H. Sobin, M.D. and Pathologists in 17 countries. 69 pages, illustrated. Geneva World Health Organization, Geneva Switzerland, 1977. Price $86.00.

This combination of slide illustrations and companion text is the best put out by the WHO. It is a superb take-off for a very informative seminar on intestinal cancer pathology and of great usefulness in the teaching programs of students, residents and fellows in general medicine, surgery, gastroenterology and oncology. I used the set on my students with great success.

DAVID A. DREILING, M.D., F.A.C.G.

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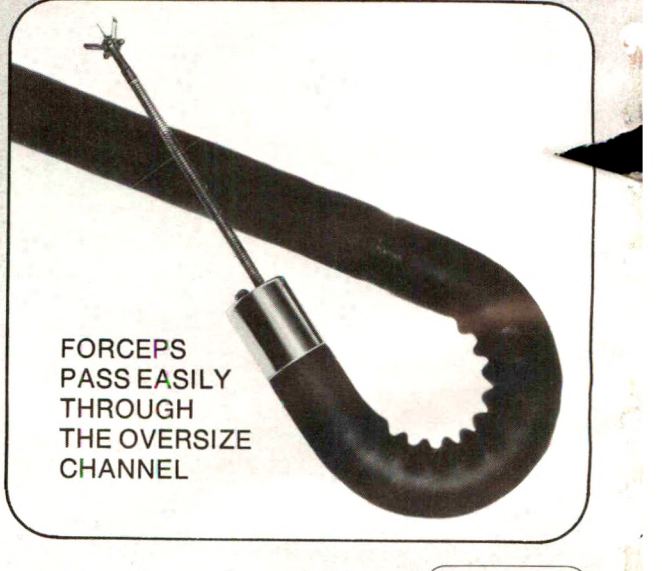
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